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EDITORIAL

THE lot of the medical student is not a happy one, and it would be unkind to suggest any addition to the list of subjects which make up his curriculum. For the general practitioner, and perhaps more so for the specialist, however, a knowledge of the history of medicine is not merely of academic interest, but of real practical value. Those who read the book on the history of tuberculosis and the chapters on tuberculosis written by Johannes de Mirfeld, both of which are reviewed in this number of the Journal, must be struck by the very slow advance of our knowledge of tuberculosis. Cough, the character of the sputum, cavities, clubbing of the fingers, wasting, night sweats were all known to the ancients as manifestations of tuberculosis. Rest was recognised as an important factor in treatment, and if certain strange and unpleasant concoctions and ablutions were advocated, who are we to judge? We have passed the age of witchcraft, but only just, and there are still those living who believe that a potato carried in the pocket will cure warts or that the rust which appears on the finger if one wears an iron ring is rheumatism coming out of the system.

The human being, naturally gullible, is apt to become more so as hope ebbs during the course of a long heart-breaking disease like tuberculosis, and to encourage the exploitation of so-called cures by the unscrupulous, who say with the father of Ung, " Son that can see so clearly, rejoice that thy tribe is blind " (*The Seven Seas*). It is not always a case of exploitation, for many " cures " are quite genuine in the sense that their advocates believe in them, and yet when we review the countless drugs and preparations that have been and are still recommended in the treatment of tuberculosis, we

may well ask ourselves whether our descendants will view our "cures" with the same amazement as we regard those of our ancestors.

What, we may ask, is the future of thoracoplasty? Already some surgeons complain that it merely compresses the lung laterally, and so advocate apicolysis in addition to an upper stage thoracoplasty.

It is said that the expectation of life is poor if the patient has an unclosed cavity in the lung and it seems certain that an unclosed cavity is a potential danger although some patients live for many years with large dry cavities.

It seems hard to believe that no less drastic methods of closing these cavities will be found. If the prospects for the patient with a cavity are bad, what are they for the patient who has had thoracoplasty or thoracoplasty and apicolysis? Time alone will show. So far evidence goes to show that thoracoplasty in a well chosen case does definitely prolong life.

Again, can the time be too far distant when treatment will be directed to prevent the development of cavities rather than to await their appearance before starting any serious treatment?

To turn to medical treatment we may wonder if there is any likelihood of the discovery of some drug which will have the slightest influence on the tuberculous lesion, or if one will be found to increase definitely the resistance of the patient. Gold was used many years ago and is again going through a phase of popularity, but it's exact value is still a matter of debate.

We are apt to forget the great men who perhaps died young, but did a full life's work in spite of being consumptive in the days before collapse therapy was employed and before the tubercle bacillus had been found. No doubt to-day under modern methods more consumptives are able to live active and useful lives, but let us give credit to the physicians who enabled such men as R. L. Stevenson, Chopin, Laennec and many others to carry out their work and to leave great names.

We do not suggest that no progress has been made, and the last thing we wish is to throw scorn on modern methods, but we say emphatically that the time has not come when we can rest on our oars, because we have yet to find a cure for consumption.

PROBLEMS IN APPLIED MEDICINE

SENILE PULMONARY TUBERCULOSIS

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PULMONARY tuberculosis has not been regarded as one of the evils to which old age is heir. A more detailed study of mortality rates and an increased use of radiology in the routine examination of the chest are changing our ideas in this respect.

A study of the textbooks devoted to diseases of the chest yields very meagre information. The reason for this is readily understood, when it is realised that abnormal physical signs in the chests of the aged are masked by shallow breathing, and in a great number of cases by the presence of emphysema.

With life already threatened by the natural decay that ends the existence of those fortunate in escaping disease, the advent of pulmonary tuberculosis offers a problem complicated beyond all hope of solution by the weakened heart, the sclerotic kidneys, and the hardened arteries.

The problem, then, is not one of diagnosis to ensure correct treatment, but to protect others from infection.

From the long history obtained in most cases it would appear that senile pulmonary tuberculosis is a chronic disease originating in early life. This theory is supported by the radiological picture, which shows an intense bilateral fibrosis. The post-mortem evidence is scanty, but the few cases examined have shown cavities surrounded by thick fibrous walls. E. Braun[1] noted that a terminal miliary tubercular state is commonly found in old persons; this should not be taken to mean that a primary infection has occurred. Wingfield[2] states "the third or old age type (of pulmonary tuberculosis) . . . is only found in districts where mining is the staple industry." This third type is an epidemiological distinction based on a study of mortality rates in different communities, and is probably secondary to silicosis.

It is probable that senile pulmonary tuberculosis is a chronic disease

originating in early or middle life, and not a primary infection of old age, whose characteristic course is altered by the slow tempo and altered metabolism of old age.

History.

The patient gives the history of a cough, which has been present for many years. The cough is mild, productive of a varying amount of morning sputum, and is usually worse in the winter.

Dyspnœa is present in a large number of cases. Occasional hæmoptyses occur, and are more commonly slight in amount.

As the disease progresses, and more especially as age advances, symptoms of cardiac failure become evident, until they dominate the clinical picture.

All forms of tubercular complications may occur, as in earlier life. Fishberg[3] stresses the frequency of diarrhœa as a symptom.

On examination evidence of focal disease of the lung is usually masked by the presence of emphysema and by the shallow breathing of old age. Asymmetry of the chest may lead to the suspicion of fibrosis, and the presence of clubbing of the fingers occasionally points to some bronchial dilatation which is found to be secondary to a tubercular fibrosis. Tachycardia is common and occasional rises of temperature occur.

The patients are usually thin and markedly under weight.

Differential Diagnosis.

Chronic bronchitis is more commonly mistaken for senile phthisis than any other disease, and it is only the radiograph of the chest and a positive sputum that will lead to a correct diagnosis. Hæmoptysis in old age is usually attributed to a carcinoma of the bronchus until routine examination suggests some other cause. In the terminal stages heart failure, secondary to a chronic bronchitis or to broncho-pneumonia, is the condition suggested by the clinical picture.

Diagnosis.

As long as the condition of pulmonary tuberculosis is borne in mind as a possible explanation of the chest symptoms, then the diagnosis should not present much difficulty.

As already stressed, the diagnosis can only be made with certainty by radiography of the chest and examination of the sputum. These investigations should be carried out in all cases in which there is or has been some condition suggesting a tubercular complication, and in any case where pulmonary tuberculosis has occurred in members of the same household, and in all cases of chronic cough occurring in individuals who are in close contact with younger persons. The disease pursues the even tenor of its

way, and it is only the incidence of some complication that persuades the patient or his doctor that a more detailed examination is necessary.

Many cases have been discovered by the examination of contacts; others, by the examination and radiography of the chests of old persons found to have laryngeal tuberculosis.

Geoffrey Marshall[4] says that "a radiogram reveals such widespread mottled infiltration of both lungs that it seems incredible that good clinicians can detect none of the characteristic physical signs of pulmonary inflammation."

Fishberg is equally emphatic on the necessity of an examination of the sputum and an X-ray of the chest.

Prognosis.

In assessing the prognosis, it should be remembered that the disease is chronic and only slowly progressive. Other factors play an important part; the general condition of the patient and the state of the heart are as relevant as the degree of involvement of the lungs.

The presence of the pulmonary tuberculosis makes the patient more liable to succumb to an intercurrent acute infection.

The presence of even a slight degree of cardiac failure is serious, and life is unlikely to be prolonged more than a few months.

Treatment.

Special attention should be paid to the hygiene of the sputum, so as to protect young contacts from sources of infection. Sputum mugs should be used. Sanatorium treatment is not necessary, since old age has curtailed the patient's activities. Cod-liver oil and malt to increase the patient's weight may be given, and an expectorant cough mixture. Sleep, fresh air and good food should be provided, but as much attention should be paid and treatment given to the heart as to the lungs.

As stated in the introduction, the diagnosis of senile pulmonary tuberculosis is important, so as to attempt to check the spread of tuberculosis, rather than the attempt to heal the disease in a subject nearing the end of the normal span of life.

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GENERAL ARTICLES

CHRONIC DIFFUSE BRONCHO-PNEUMONIA

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ACCURATE diagnosis of chronic pulmonary diseases has been much facilitated by the development of radiology. The help thus obtained is especially relied upon in the diagnosis of pulmonary tuberculosis. A group of three cases, recently observed at the Brompton Hospital, in which both clinical and radiological evidence were very suggestive of a diagnosis of pulmonary tuberculosis, negatived at autopsy, therefore seems worthy of record. In addition, the combination of clinical and pathological features found in these cases appears to be uncommon.

CASE 1.—Mrs. E. C., aged twenty-six years, was first admitted to Brompton Hospital under the care of Dr. Gosse on January 10, 1934.

She was complaining of a cough, accompanied by scanty muco-purulent sputum, which had developed during her last pregnancy in 1932 and had persisted. In September, 1933, she had had a small hæmoptysis on one occasion only. Recently she had noticed some dyspnœa on exertion; there had been some loss of weight.

The previous history showed nothing of note. In the family history it was noted that her mother had died of phthisis in 1932. She had three children, all well, the youngest aged two years.

On admission she was a slightly built woman, with evidence of recent loss of weight. Her present weight was 91 pounds.

The fingers showed early clubbing.

The evening temperature was elevated to 99° F., the morning temperature being rather subnormal, giving a large diurnal swing. Examination of the chest showed slightly diminished movement of the right side, with impaired percussion note and a few scattered râles on this side.

The upper respiratory tract showed an atrophic rhinitis. Examination of other systems was negative.

The sputum, which was scanty and muco-purulent, was examined four times for tubercle bacilli with negative results.

X-ray of the chest (Fig. 1) was reported upon as follows:

"Heart and mediastinum displaced to the right side.

"Right-sided pleural thickening.

"Coarse mottling in all zones of both lungs, with evidence of fibrosis in the right middle and lower zones."

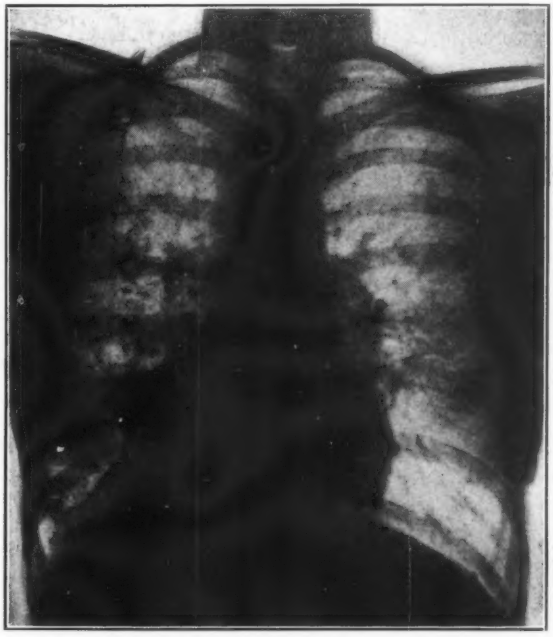

FIG. 1.—CASE 1, JANUARY 12, 1934.

Lipiodol was injected into the bronchial tree, and showed no evidence of dilatation of the bronchi outlined.

In hospital she improved, becoming afebrile and gaining 4½ pounds in weight. A provisional diagnosis of fibrosis of the lung was made, and she was transferred to a convalescent home.

On November 21, 1934, she was readmitted. She had remained under the care of the tuberculosis officer for her district: he reported rapid deterioration in her condition, and had had a further X-ray examination performed. This had been reported to show definite evidence of tuberculosis, although repeated sputum examinations were always negative.

On readmission it was found that the cough was much worse, and was

now accompanied by copious purulent offensive sputum. The dyspnœa was much increased. Marked wasting was evident. The temperature chart showed irregular maintained fever between 101° and 103° F.

Sweating was troublesome.

On examination the impairment of movement and percussion note on the right side was more marked. Auscultation revealed numerous rhonchi and râles scattered all over both lungs, the râles being more numerous on the right side.

The clubbing of the fingers had increased.

Examination of other systems was still negative.

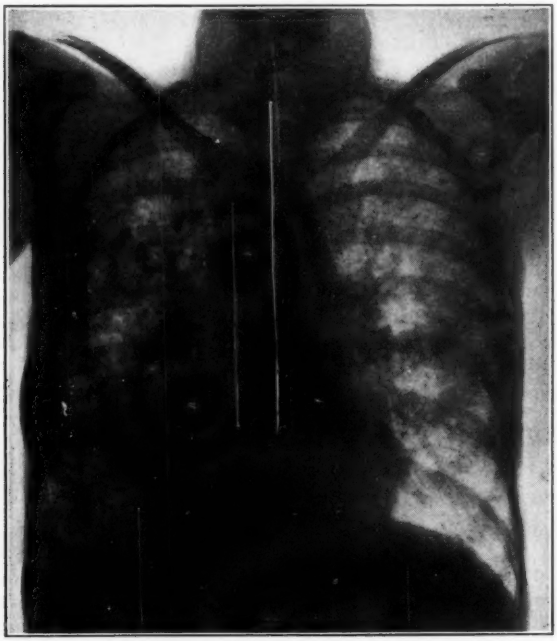

FIG. 2.—CASE 1, NOVEMBER 26, 1934.

The sputum was again examined for tubercle bacilli on four occasions with negative results.

X-ray examination (Fig. 2) showed:

"There is now considerably more mottling in both lungs, and evidence of cavity formation in the lower zone of the right lung."

Her downhill course in hospital was rapid. Dyspnœa increased, with increasing difficulty in expectoration of the copious purulent sputum, cyanosis became evident, and she died on November 27, six days after her second admission.

At autopsy the significant findings were confined to the thoracic organs.

The pericardium contained an excess of clear fluid.

The heart showed slight dilatation of the right side.

The right pleura was firmly adherent over the upper half; the left pleura was free of adhesions.

Lungs.—Scattered throughout the right lung were a few small thin-walled cavities, mostly about 5 mm. in diameter, but a few larger, up to 10 mm. in diameter. One in the upper lobe was seen to communicate directly with a bronchus. Round some of the cavities there was a good deal of induration, making them hard to the touch, and some were the centres of definite patches of red consolidation. The induration was not part of the wall of the cavity, but was a surrounding pneumonia. Thin strands of fibrous tissue were scattered about. The terminal branches of the main descending bronchus appeared to be a little dilated. The left lung showed similar appearances on a less extensive scale.

The tracheo-bronchial glands showed enlargement of a septic type, more marked on the right side; one of them on the right side contained two small abscesses, a smear from which showed the presence of Gram-positive diplococci. The mediastinal glands were also slightly enlarged.

Histologically, the cavities were found to be small chronic abscesses. The condition of the lung was one of pneumonia in various stages. Some alveoli were still full of red cells, and in a state of recent consolidation. In most places resolution was proceeding; in some it was almost complete, in others it was actively progressing, with macrophages removing the red cell exudate. The walls of many alveoli were thick with chronic inflammatory cells, and fibrosis was occurring. The process of organisation had given rise to scattered thick fibrous strands. The broncho-pulmonary and tracheo-bronchial glands were found on section to show simple chronic inflammation.

Case 2.—G. S., male, aged thirty-one, a railway engine driver, was admitted to Brompton Hospital under the care of Dr. Wall on August 15, 1934. He had had no serious illness in his life until April 9, 1934, when he was attacked by a sudden febrile illness, commencing with a rigor and sweats and pleuritic pain on the right side. This was diagnosed as pneumonia, and apparently settled down satisfactorily, for after some weeks he was sent into the country to convalesce. However, dyspnœa on exertion and slight cough with expectoration continued, and on July 16 he was again confined to bed on account of pain in the right side of the chest, and one or two small hæmoptyses, amounting to staining of the sputum only. The sputum at this time was found to be negative for tubercle bacilli; on culture, a pneumococcus and micrococcus tetragenus were isolated from it. Evidence of fluid in the right pleura was found, and on needling clear fluid was obtained. He was therefore referred to the Brompton Hospital for diagnosis.

His family history showed nothing of note.

On admission he was thin, but not wasted; dyspnœic on slight exertion; febrile, the temperature ranging irregularly from 99° to 101° F.; and there was slight clubbing of the fingers.

On examination of the chest there was dullness, diminished voice conduction and weak breath sounds at the right base. There were no added sounds on the right side, but on the left side pleural friction was audible in the axilla.

Examination of other systems was negative.

The sputum was muco-purulent, a trace to one drachm daily, and no tubercle bacilli were found on repeated examinations.

X-ray of the chest (Fig. 3) showed:

" Heart and mediastinum in normal position.

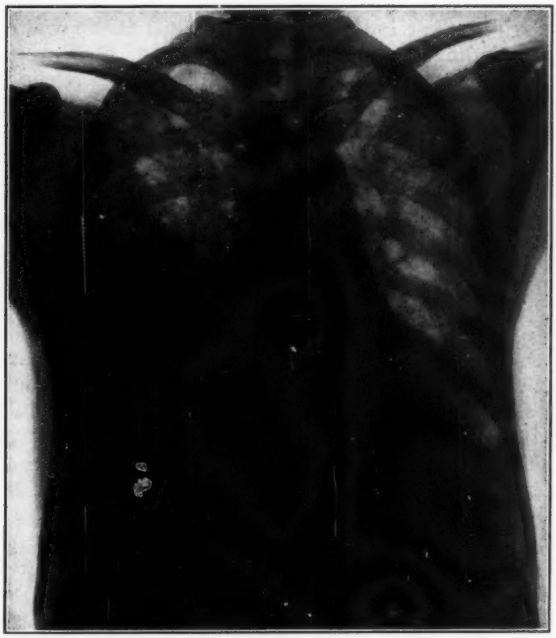

FIG. 3—CASE 2, AUGUST 16, 1934.

" Right lung: Infiltration in all zones with pleural involvement at the lower zone.

" Left lung: Infiltration of all zones."

On August 27 very little change was noted in the general condition. The signs of fluid at the right base had increased somewhat, and on needling 250 c.c. of clear amber fluid was aspirated from the right pleura. Examination of this revealed that it was sterile, negative for tubercle bacilli, and contained a few lymphocytes only.

At the beginning of September he was clearly going downhill; although the temperature remained about the same, the pulse-rate had risen from

84-90 to 90-100 ; and physical signs suggested the presence of a small effusion in the left pleura also. A blood count showed :

Erythrocytes	.. ..	4,500,000	
Hæmoglobin	.. ..	78 per cent.	
Colour Index	.. ..	0·89	
Leucocytes	.. ..	16,200	
Polymorphs	.. ..	69 per cent.	
Lymphocytes	.. ..	25 per cent.	
Mononuclears	.. ..	3	,,
Eosinophils	.. ..	2	,,
Basophils..	.. ..	1	,,

By October, the amount of sputum had steadily increased to 5 to 7 ounces daily, and it had become purulent. Cough was difficult, and dyspnœa troublesome. Progressive wasting was evident. The pyrexia gradually assumed an irregularly swinging character from 97° to 102° F., the pulse-rate increased to the region of 130, and on November 13 he died.

The chief autopsy findings were as follows :

The pericardium contained some clear fluid ; the heart was flaccid and dilated.

The right pleura was much thickened and adherent everywhere except for a transverse slit about an inch broad containing a little pus. The left pleura was universally adherent.

The right lung showed an area of red consolidation in the upper part of the lower lobe; a few small yellowish nodules were distributed throughout the lungs. Pus could be squeezed from several points in the consolidated area. The left lung showed almost identical lesions.

The tracheo-bronchial glands were slightly enlarged, soft and septic.

The liver showed a suppurating blackish area posteriorly on the right lobe about the size of a large plum, and the gall-bladder was distended with foul-smelling juice.

The spleen was soft and septic.

On bacteriological examination the pus from the right pleura and from the liver gave similar findings; it was negative for tubercle bacilli, showed no bacteria in a direct smear, and on culture yielded only a coliform organism which may have been a contaminant.

Histological sections were taken from the left lower lobe near the base, and from an area of apparent red consolidation at the base of the right upper lobe. In each section, resolving pneumonia was the essential lesion. It was of a patchy distribution; in some parts normal resolution was evident; there were some small foci of polymorphonuclear cell infiltration, not proceeding to gross abscess formation; and in some places, especially in the lower lobe, fibrous tissue was being laid down. Several small bronchioles were seen to be disorganised, and contained numerous pus cells.

Case 3.—A. P., male, aged forty-eight, a shop assistant, was admitted to Brompton Hospital on December 24, 1934, under the care of Dr. Burrell.

He gave a history of having had small hæmoptyses in 1905, 1909 and 1911. He was in receipt of a 50 per cent. Army pension for "bronchitis." In 1924 he had a rather more severe hæmoptysis, but apparently had no special treatment. In 1926 he had pneumonia, and in 1932 a severe attack of influenza was followed by another hæmoptysis.

The present illness began in September, 1934, with a fall, apparently on the right side of the chest, followed by pain in this region. He carried on with his work until the end of November, when pain in the right side of the chest, dyspnœa on exertion, increase in the cough and expectoration which he usually had in the winter, and general malaise caused him to be confined to bed.

In his family history there was nothing of note.

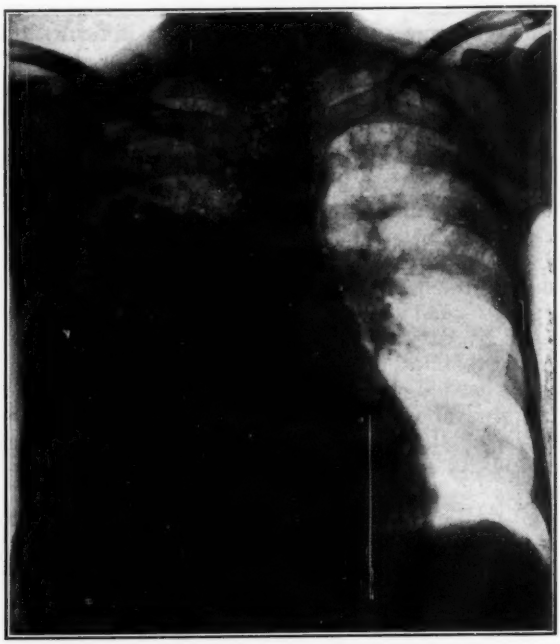

FIG. 4—CASE 3, JANUARY 2, 1935.

On admission he was obviously ill, dyspnœic, slightly cyanosed, and apathetic. This rendered it very difficult to obtain a full history.

There was no clubbing of the fingers.

The temperature was swinging from 98° to 102° F.

On examination the heart was in normal position, with normal sounds, blood pressure 140/80. The chest was rigid; percussion note was generally poorly resonant, with dullness at the right base, showing a shifting upper level high in the right axilla. The breath sounds were weak all over the right side, and scattered rhonchi and râles were audible over both lungs.

Examination of other systems was negative.

The sputum was purulent in character, amounted to 2 ounces daily, and on two examinations no tubercle bacilli were found.

X-ray examination (Fig. 4) showed:

" Heart and mediastinum displaced slightly to the left side.

" Right lung: Opacity in all zones, especially middle and lower, with a fluid level (in the erect posture) opposite the second rib anteriorly.

" Left lung: Suspicious mottling of the middle zone."

On January 4, 1935, the right pleura was needled in the fifth space in mid-axilla. Twelve ounces of slightly malodorous pus was aspirated. On examination this was negative for tubercle bacilli, and grew *Diplococcus flavus* on culture.

In view of the X-ray report, the history of repeated hæmoptyses, and the

FIG. 5—CASE 3, JANUARY 8, 1935.

absence of the usual pyogenic organisms from the pleural pus, the most probable diagnosis was thought to be pulmonary tuberculosis with spontaneous pneumothorax, leading to a septic pyo-pneumothorax with pleuro-bronchial fistula, in spite of the failure to demonstrate the presence of the tubercle bacillus. On January 6 an intercostal drainage tube was inserted at the site of the previous aspiration; 14 ounces of thick offensive pus escaped, and the tube was connected to an under-water drainage bottle.

An X-ray examination on January 8 (Fig. 5) showed:

" Right lung: The fluid level has disappeared.

" Left lung: Coarse mottling of all zones."

The spread of the radiological infiltration in the left lung seemed to support the tentative diagnosis of pulmonary tuberculosis, but further examination of the sputum failed to reveal the tubercle bacillus.

In spite of free drainage (5 to 8 ounces daily), improvement was temporary only, and the swinging pyrexia continued. He gradually became weaker, the pulse-rate rose, and he died on January 10, 1935.

The main autopsy findings were:

The pericardium contained a little clear fluid. There was a tough band adhesion to the left ventricle.

The right side of the heart was slightly dilated, and the aorta showed slight atheroma.

The right pleura was firmly adherent over the upper lobe, with an empyema cavity over the lower lobe, drained through a sinus in the right axilla. The lobes of the right lung were firmly adherent, and the lung was firmly adherent to the tenth intercostal space, into which a small exostosis pointed, arising from the eleventh rib—? due to old injury.

The left pleura showed recent easily separated band adhesions over the whole lung, the lobes being partly adherent.

Right lung: Thick yellow pus emerged from bronchi all over the lung. The lower lobe was nearly all broncho-pneumonic, especially in its lower half, and appeared to be turning gangrenous. Starting in contact with the interlobar septum in the upper lobe near the surface of the lung, there was a large abscess full of yellow pus, extending upwards and inwards. The cavity admitted a finger for about one inch. The upper lobe was aerated, but the lung was generally œdematous.

Left lung: Pus could be squeezed from the bronchi, and there were patches of broncho-pneumonia in the lower lobe, and the lung was generally œdematous.

The tracheo-bronchial and mediastinal glands were enlarged and of septic type.

The liver showed a nutmeg pattern. On its diaphragmatic surface were three deep sulci, corresponding with linear adhesions between the base of the right lung and the diaphragm.

Examination of the pus from the abscess in the right upper lobe showed streptococci, and was negative for tubercle bacilli.

Histologically, a section from the right lower lobe showed some recent red consolidation, many areas of resolving pneumonia, much chronic inflammation, and foci of suppuration in the lung parenchyma. The pleura was thick, vascularised, and fibrous. A small bronchus and bronchioles contained pus, their walls were infiltrated with chronic inflammatory cells, and some desquamation of the mucosa was evident.

Discussion.

These three cases appear to be associated in a common group by clinical, radiological, and pathological features. Clinically, they were characterised by a subacute to chronic course, the duration of symptoms from onset to

death being two years, seven months, and three and a half months. Cough was an initial symptom in all cases; it was accompanied by sputum which, at first scanty and muco-purulent, gradually increased in amount and became frankly purulent. Small hæmoptyses occurred in all cases. Dyspnœa was prominent and was steadily progressive. Pleurisy was a feature of cases 2 and 3; it was followed by a clear, lymphocytic effusion in case 2, and by purulent effusion in case 3. Fever and parallel increase in pulse-rate were present; the fever was of no very constant type. During the earlier stages of case 1 only very slight or no pyrexia was present, but a rather marked diurnal swing was observed. In the terminal stage of this case the pyrexia was sustained. In cases 2 and 3 an irregularly swinging pyrexia was observed throughout.

Radiologically, the common factor between the three cases is the presence in all of mottling of such a type as to cause suspicion of tuberculous infiltration. The increase of this mottling in the chronic case 1 and the acute " woolly " spread to the left middle zone observed in the more acute case 3 form interesting parallels to the similar changes observed in the progressive course of pulmonary tuberculosis.

Pathologically, in each case the essential lesion is simple pneumonia in varying stages of evolution. The only unusual features are the diffuse distribution of the lesions through both lungs and the presence in different foci of all stages of pneumonia—early consolidation, resolving consolidation, organisation, and suppuration. Although on section the autopsy specimens showed much inflammation of the small bronchi and bronchioles, the larger bronchi appeared to be relatively unaffected, and there was no evidence of bronchial dilatation, except to a very mild degree in the chronic case 1. A correlation of the clinical, radiological, and autopsy findings suggests that the underlying pulmonary lesion is essentially a diffuse broncho-pneumonia in rather small foci, showing an unusual variety of modes of progress and spread, progress being towards resolution in some foci, towards organisation leading to fibrosis in others, and towards suppuration leading to minute abscesses in others; spread being not only by local extension but also, on the evidence of radiological examination in cases 1 and 3, by the appearance of fresh foci in previously unaffected areas of lung.

A survey of the literature revealed very few reports of comparable cases with autopsy records. A few more cases have been recorded in which clinical and radiological features were similar, but recovery occurred. There seems to be no reason why a condition whose pathology is that outlined above should not resolve completely at almost any stage, with more or less residual fibrosis. It seems therefore justifiable to include these recovered cases in the same group even in the absence of the conclusive proof of autopsy evidence.

Oberndorfer[1] reported the case of a man of fifty-six years, previously healthy, whose symptoms on first coming under observation were cough and sputum and increasing dyspnœa of one month's duration. He had had occasional blood-staining of the sputum. Clinically and radiologically an area of consolidation in the right middle zone, going on to abscess formation, was found. In the left lung, radiological examination revealed the presence of diffuse fine mottling throughout. A fortnight later this mottling had become more distinct, and the process in the right lung had progressed. He died two months from the onset of symptoms. Autopsy revealed multiple abscess cavities with organised pneumonic walls in the right lung. In the left lung no macroscopic change was found; but on histological examination all parts of the left lung except the apex were found to contain numerous foci consisting of irregular collections of alveoli in a state of consolidation, some fibrinous, but mostly cellular and containing vascular connective tissue. Oberndorfer called the condition "miliary organising pneumonia" and concluded that though rare it should be thought of when miliary radiological shadows occur in the absence of other evidence of pulmonary tuberculosis; but he remarks that diagnosis can be made only on histological examination.

Peschel,[2] discussing the radiological appearances of atypical influenzal pneumonia, refers to a patient who, shortly before dying of gastric carcinoma, had a subacute pulmonary affection characterised clinically by subfebrile temperature, cough, dyspnœa and cyanosis, with physical signs of acute bronchitis. X-ray examination showed enlarged hilum glands and scattered, rather coarse mottling through both lungs, which led to a diagnosis of secondary deposits in the lung. The mottling, however, largely cleared within ten days. At autopsy a condition described as miliary broncho-pneumonia, the foci showing central hæmorrhage and abscess formation, was found. Peschel remarks that similar pathology may account for reported cases of healed miliary tuberculosis.

A case reported by Münchbach[3] makes an interesting comparison with case 2. Though his case recovered, the clinical and radiological features, combined with the occurrence of a clear lymphocytic effusion, render the similarity between the two cases striking.

The patient was a male aged nineteen years. He gave a history of the insidious onset, over five months, of dyspnœa, cough, anorexia and sweats. There was no pyrexia. A skiagram of the chest showed scattered mottling with foci 2 to 3 mm. in diameter, appearing confluent in places, in both lung fields; but examination of the sputum was negative for tubercle bacilli. Two months later the temperature rose to 38° C., and left-sided pleuritic pain, accompanied by a rub, occurred. A month later the temperature had risen still higher, and an effusion formed at the left base. This was found to

be clear serous fluid, containing lymphocytes. On culture pneumococci were found. These organisms were also isolated, and proved by mouse inoculation from blood, urine, and sputum; the latter was shown to be free of tubercle bacilli by guinea-pig inoculation. Shortly after this a further X-ray examination showed no change in the mottling, the effusion being shown at the left base. In the course of the next two weeks the effusion slowly absorbed spontaneously, and slow general improvement started. Three years from the onset he was well, and a skiagram showed only some left basal pleural thickening, the parenchyma being clear. Thums[4] records a rather similar case of shorter duration. The patient was a woman aged thirty-six years, whose chief symptoms were cough and fever. There was a history of contact with phthisis. Three weeks from the onset, X-ray of the chest showed " small soft foci diffused through the lungs," the right being more affected than the left, especially at the hilum, and the apices more than the bases; and a small effusion at the right base. The appearances resembled those of miliary tuberculosis, but tubercle bacilli were never demonstrated in the sputum. Two weeks later, a small effusion appeared at the left base. In the sixth week the temperature fell suddenly, and on radiological examination the foci had notably diminished in number. In three months from the onset the radiological picture had returned to normal.

Heesen[5] described a case which at the time of his report had pursued a chronic course for eighteen months. Though the evidence in this case is not conclusive, it shows a striking similarity to case 1. The patient was a woman of thirty years, whose illness pursued a relapsing course. Her chief symptoms were cough, sputum, recurrent bouts of fever, two attacks of left-sided pleurisy with clear effusion, lassitude, loss of weight, and night-sweats during the febrile episodes. The sputum tended to increase in amount and became more purulent and offensive during the period of observation. Radiologically, the chief feature was wandering consolidation leaving fibrosis, especially at the right base, the appearances very strikingly resembling those of case 1. Examination of the sputum and pleural fluid failed to demonstrate tubercle bacilli even after animal inoculation. On one occasion, culture of the sputum showed enterococci to be the predominant organisms, hæmolytic streptococci, staphylococci, and influenza bacilli being also present. On this rather slender evidence, Heesen incriminates the enterococcus. Whatever the causative organism, it seems reasonable to place this case in the group of the chronic diffuse broncho-pneumonias.

Unfortunately, the bacteriological evidence available in the present series is very limited. From the information available, and from case reports in the literature, it appears likely that no specific organism can be implicated in these cases of chronic diffuse broncho-pneumonia, any of the organisms

causing pneumonia being capable of producing a diffuse chronic reaction. Presumably the determining factors in producing such a reaction are the resistance of the patient to the infection and the anatomical distribution of the lesion. In this connection it is interesting to note that there have been recorded cases in which it is probable that an acute pneumonic lesion of the same distribution has been present. The difference between the acute and chronic groups of cases must be related to the differing resistances of the patients. As to the factors which, both in the acute and the chronic cases, give rise to the unusual anatomical distribution of the lesions, there appears to be no clue.

Acute Diffuse Broncho-Pneumonia.

Acute cases of diffuse broncho-pneumonia in which radiological as well as clinical confusion with miliary pulmonary tuberculosis occurred are recorded by many observers, especially in children. Sante[6] refers briefly to a case of " miliary broncho-pneumonia " radiologically indistinguishable from miliary pulmonary tuberculosis. Wessler and Jaches[7] mention an apparently similar case, which they term " universal broncho-pneumonia." Blechschmidt, Perlmann and Cohen[8] describe the case of a boy of nine and a half years in which a clinical syndrome of recurrent frontal headache, cough, vomiting, dyspnœa and cyanosis with a high leucocyte count was accompanied by a radiological picture indistinguishable from that of miliary pulmonary tuberculosis. Complete recovery occurred within five weeks of the onset, and they considered the condition to be one of " acute disseminated broncho-pneumonia." Liebmann and Schintz,[9] describing the X-ray picture of influenzal pneumonia, recognise a miliary broncho-pneumonic type, though none of their cases showed a widespread distribution of this type. The case of Peschel,[2] to which reference has already been made, would probably fall into this group, and affords autopsy evidence which is lacking in the other cases of the group.

Differential Diagnosis.

Consideration of the cases here reported, and of the similar cases collected from the literature, leads to the conclusion that there is a group of cases of chronic diffuse broncho-pneumonia which may form a recognisable clinical entity. Its clinical and radiological manifestations are quite distinct from those of the usual type of unresolved pneumonia, and from those of the rarer forms of chronic pneumonia that have been reported; they closely resemble those of some forms of pulmonary tuberculosis, and it is from the latter condition that differential diagnosis is most important. Some points in the differential diagnosis of these various conditions will therefore be discussed.

1.—Unresolved Pneumonia.

The difficulties occasionally presented by the differential diagnosis between slowly resolving pneumonia and pulmonary tuberculosis are well known and have been widely discussed. In the usual type of slowly resolving pneumonia, if difficulty is experienced it is mainly clinical, radiological examination speedily clearing up the diagnosis by demonstrating the characteristic, rather homogeneous opacity of unresolved pneumonia. Fishberg[10] recognises acute and chronic types of unresolved pneumonia, and states that difficulty in diagnosis is practically confined to those running an acute course. He states that " the differentiation of these cases from phthisis is made first by taking cognizance of the location of the lesion. Basal lesions in tuberculous patients are extremely rare; when they do occur they are of the exudative variety, and as such clearly seen on the roentgen film. In the rare cases showing involvement of the upper lobe, it will be noted that auscultatory phenomena are pronounced, while on the roentgen film no changes characteristic of tuberculosis can be seen." This view well represents that of most of the standard text-books. Numerous cases are reported, however, in which the radiological picture of a slowly resolving pneumonia temporarily simulated tuberculous infiltration of the lung. In most of them the subsequent course was towards complete resolution, and the diagnosis was in doubt for a short time only. In this category may be placed the cases recorded by Rist and Blanchy,[11] in which, following pneumonia, an apical mottling was observed to be present for nine months, but eventually cleared completely; and by Cain, Oury and Barnaud,[12] in which an acute onset with rigor, cough, and pleuritic pain at the left base was followed by pyrexia and purulent expectoration, the skiagram showing remarkable coarse mottling at the right base. In the latter case the diagnosis was decided by the clinical course, the temperature settling by lysis and the skiagram becoming clear after four weeks. Many similar cases have been reported. The feature which distinguishes the normal type of unresolved pneumonia from the cases described in this paper is the more uniform behaviour of the former: a well-defined consolidated area tends towards a uniform slow resolution or fibrosis, or, more rarely, abscess formation, there being little tendency for the consolidation to spread to fresh areas once the acute phase is ended. These points are well shown in the radiological studies of lobar pneumonia of Graeser, Wu and Robertson,[13] and of Davies, Hodgson and Whitby.[14] The former writers state that " the resolving shadow may closely simulate pulmonary tuberculosis, but rarely persists long enough to confuse the diagnosis."

2.—Other Forms of Chronic Pneumonia.

Several observers have reported cases of chronic pneumonia in which the *Bacillus mucosus capsulatus* of Friedländer has been regarded as the causative organism. Collins and Kornblum[15] report three such cases. The clinical course was characterised by a tendency to relapses; hæmoptysis was a prominent symptom in two of the cases, and the consolidation had a marked tendency to suppuration, causing lung abscesses, which drained well through the bronchi and healed themselves. All three cases recovered with some residual fibrosis after three to six months' illness. The anatomical lesion appeared to be a migrating lobar pneumonia with a tendency to multiple abscess formation in the affected lobes. The bacteriological diagnosis was made by the finding of Friedländer's bacillus in pure culture in the sputum. The author concluded that chronic Friedländer pneumonia was a definite entity which might simulate pulmonary tuberculosis.

In an article reporting eighteen cases of Friedländer pneumonia, Belk[16] describes three chronic cases which simulated pulmonary tuberculosis. They were all fatal, and again the Friedländer bacillus was isolated without difficulty, both ante- and post-mortem.

Although, unfortunately, complete bacteriological investigations were not performed in the cases here described, in no case was Friedländer's bacillus found, whereas in the cases of Collins and Kornblum and of Belk this organism was demonstrated repeatedly with ease; moreover, in their cases the lesion was typically of lobar distribution, and radiologically therefore less similar to pulmonary tuberculosis.

Hecht[17] has described a chronic "giant-cell pneumonia" in infants, which may have a clinical course of several months. The essential histological feature of the condition was the presence in the alveolar exudate of numerous large foreign-body giant cells. Dugge[18] has reported a case in an adult showing similar histological features. These rather striking features were absent from the present series.

3.—Pulmonary Tuberculosis.

The accurate diagnosis of non-tuberculous chronic lung infections is obviously important in view of the many personal and social implications of a diagnosis of tuberculosis. When a case presents a clinical picture of a chronic lung infection, combined with a radiological picture of mottling of the type usually associated with tuberculosis, it is difficult to avoid a diagnosis of the latter condition, even in the persistent absence of tubercle bacilli from the sputum.

In any large group of cases of chronic phthisis there will usually be found a few examination of whose sputum has always failed to show tubercle bacilli, the diagnosis having been made on clinical and radiological grounds. It is an interesting speculation how many of these cases are really cases of chronic non-tuberculous diffuse pneumonia. Occasionally, as in the case of Heesen[5] to which reference has already been made, some feature of the clinical or radiological picture appears unusual, and the diagnosis of tuberculosis is rejected. But however probable the diagnosis of a chronic simple pneumonic process may seem in such a case, it must remain a matter of inference until autopsy evidence is obtained. Even in the numerous cases in which the diagnosis of pulmonary tuberculosis has been amended on account of unexpected resolution, the amended diagnosis is inferred rather than proved.

An analysis of the factors which may cause a case of pulmonary tuberculosis to show signs of activity and yet not give rise to a sputum containing tubercle bacilli may be helpful in considering the differential diagnosis. Bacilli are frequently absent in the early stages of active tuberculous infiltration of the lungs, while the lesions remain closed; and they may be absent for long periods in the later stages of quiescent fibro-cavernous tuberculosis. In the latter group, although there may be no activity of the tuberculous process, symptoms similar to those of tuberculous activity may be produced by secondary infection. A combination of the two groups is also possible when a recent acute spread of disease is observed in a patient with an old chronic lesion. The picture is still further confused when there is a complication such as pleural effusion which, though causing clinical signs of activity, does not necessarily lead to the discovery of tubercle bacilli. Hence, there are quite a large number of cases in which failure to demonstrate tubercle bacilli in the sputum, even in the presence of evidence of active disease, does not negative a diagnosis of tuberculosis; and it is from these cases that cases of chronic diffuse pneumonia must be distinguished. Of the cases here reported, case 1 would need to be distinguished from a case of chronic pulmonary tuberculosis with marked secondary infection; case 2, in its earlier stages, from an acute case with pleural effusion; and case 3 from an old quiescent case with recent acute spread, complicated by pyopneumothorax.

A feature of these cases which characterised all three was a steadily increasing amount of expectoration. In each case the sputum not only increased in daily amount with the progress of the disease, but changed in character from muco-purulent to frankly purulent, so that in the terminal stages it was profuse, purulent, and even offensive. Such a progressive change in character with repeated failure to demonstrate tubercle bacilli

must be regarded in retrospect as conclusive evidence against the diagnosis of tuberculosis.

The clear lymphocyte-containing effusion which occurred in case 2 appeared to be evidence in favour of the tuberculous origin of the lesions. But lymphocytic effusions are known to occur in cases of influenzal pneumonia and to absorb spontaneously; and clear effusions are recorded in cases of pulmonary suppuration. For instance, Maxwell[19] in a survey of post-mortem records of cases of lung abscess found that of 199 cases of single lung abscess 4 had clear effusions; and also of 116 cases of multiple abscesses 4 had clear effusions. The writer has observed such effusions clinically in the course of cases of lung abscess on several occasions. They may at first contain an excess of lymphocytes, and may either absorb spontaneously or after aspiration, or may become increasingly turbid with numerous polymorphs leading on to empyema. One such patient recently under observation had a clear effusion for many weeks. The first cytological report showed numerous lymphocytes and eosinophils, with only occasional polymorphs and endothelial cells. Six weeks later, the fluid was still sterile, only very faintly turbid, but the cells were by this time mostly polymorphs, though lymphocytes were still present. The fluid eventually absorbed completely. In the artificial pneumothorax treatment of lobar pneumonia, effusions occur which may remain clear and sterile. In a series of 42 cases so treated, Blake, Howard and Hull[20] encountered two sterile clear pleural effusions, large enough to need aspiration; one of these was present for four weeks, and both eventually absorbed completely. The cytology of the fluid in these cases is not recorded. In the case recorded by Münchbach,[3] referred to previously, a clear lymphocyte-containing effusion was shown to contain pneumococci and yet absorbed spontaneously. In case 2, although the effusion had absorbed almost completely at the time of death, at autopsy there was a small pocket of pus in the pleura. Probably, therefore, in the chronic pneumonic conditions, as in lung abscesses, there is a tendency for an effusion to become purulent eventually, even if it is at first clear and lymphocytic. Tuberculous effusions may also become purulent even in the absence of secondary infection, though only very occasionally; this event, of course, is commoner in those effusions complicating pneumothorax. Thus, an effusion containing an excess of lymphocytes cannot be regarded as a reaction specific to tuberculosis. Possibly the difference between effusions due to tuberculosis and those due to other infections is one of rapidity of progress towards the purulent stage absorption occurring in most tuberculous cases before the stage of polymorph excess. However, the presence of a clear lymphocytic effusion, especially if lymphocytes remain the predominant cells, must always

be considered confirmatory evidence of the presence of a tuberculous infection.

All three of the cases here reported showed a poor response to rest in bed; the raised temperature and pulse-rate did not show the same tendency to settle with adequate rest as is so constantly observed in pulmonary tuberculosis. This feature was especially marked in case 2. Tuberculous disease of the extent and nature suggested by the radiological examination of this case would be expected to show a good response to sufficiently prolonged rest. In the reported cases which recovered, notably that of Thums,[4] the level of pyrexia apparently bore little relationship to the conditions of rest, and defervescence tended to occur rather suddenly. This absence of the expected improvement from adequate rest might be considered a helpful point in differential diagnosis from pulmonary tuberculosis.

Similarity of radiological appearances to those of pulmonary tuberculosis was most marked in case 2. In cases 1 and 3 the radiological mottling was rather coarser than that usually seen in tuberculosis, though perfectly compatible with this diagnosis. Changes in the appearances of obscure infiltrations are often most helpful in elucidating their nature, but in these cases the mottling extended and maintained its original characteristics. The existence of non-tuberculous chronic infections of the lung whose radiological appearances so closely simulate those of pulmonary tuberculosis calls for caution in the interpretation of radiological pictures suggestive but not typical of pulmonary tuberculosis.

I am indebted to Dr. Cecil Wall, Dr. L. S. T. Burrell, and Dr. A Hope Gosse for permission to report cases which were under their care; to Dr. R. L. Rawlinson for the radiological reports; and to Dr. E. E. Atkin for the post-mortem reports.

Summary.

1. Clinical, radiological, and autopsy records of 3 cases of chronic pulmonary infection are presented. During life they had closely simulated pulmonary tuberculosis both clinically and radiologically; at autopsy the essential lesion appeared to be a chronic diffuse broncho-pneumonia showing consolidation, resolution, organisation, and suppuration irregularly in different foci, with a tendency to spread to previously unaffected areas.

2. Some relevant literature is briefly surveyed.

3. It is suggested that this condition may form a recognisable clinical entity.

4. The differential diagnosis of the condition from other forms of chronic pneumonia, including unresolved lobar pneumonia, and from pulmonary tuberculosis is discussed.

5. The circumstances which may give rise to a sputum free from tubercle bacilli in active pulmonary tuberculosis, and the diagnostic significance of a clear lymphocytic effusion, are discussed.

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EXPERIMENTAL STUDIES ON EARLY PULMONARY TUBERCULOSIS OF THE "ADULT TYPE"

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"EARLY pulmonary tuberculosis" must not be confounded with the primary pulmonary lesion, the "tuberculosis of the childhood type" of American authors, which is obviously caused by the inhalation of droplets or dust of sputum, and in children with insufficient resistance may develop into acute generalised tuberculosis. Analogous conditions can also be found in adults who have escaped infection in childhood.*

* The origin of chronic generalisation in the adult—tuberculosis of the urogenital system, bones, joints, suprarenal glands, serous membranes, meningitis, etc., in the majority of cases with a peculiar picture of pulmonary involvement—is a problem requiring elucidation, which, however, will not be discussed in this paper.

But such conditions can be clearly differentiated from common chronic isolated pulmonary tuberculosis, bronchogenic phthisis, the early " tuberculosis of the adult type " of American authors, concerning the pathogenesis of which opinion is divided.

According to some authorities, the first foci of this form of the disease, especially those in the apex and infraclavicular regions (" early infiltrations "), are directly due to exogenous reinfection; according to others, they are the result of either hematogenous metastasis or coarse bronchogenic aspiration from recrudescent foci in the lung (" endogenous reinfection ").*

As a contribution to the solution of this problem, I have endeavoured to reproduce in animals tuberculous lesions analogous to those of the " adult type " of early pulmonary tuberculosis, and to infer from the mode of infection employed the usual path of bacillary invasion.

These lesions were characterised by:

1. Limitation of the process to the lungs.
2. Restriction of hematogenous foci to certain areas of the lung, especially the apex (abortive and discrete miliary tuberculosis).
3. Formation of focal confluent infiltrations with a tendency to liquefaction and multiplication by bronchogenic outspread.

About seventy rabbits were infected by intravenous or intratracheal injection of ·1-5 mg. BCG or human strains (obtained from sputum).† Six weeks after the last injection these animals were reinfected, some intravenously and others intratracheally, with ·001-·01 mg. of a virulent bovine strain,‡ ·01 mg. of which killed a normal rabbit in about forty days after intravenous injection. Some of the animals were reinfected with the human strain H37, which killed a normal animal in about forty days when injected intravenously in doses of ·1-1 mg. The H37 strain was therefore employed for primary intravenous infection in smaller dosage only, which did not elicit macroscopical foci.

In normal animals intravenous injection of the sputum and BCG strains produced either no macroscopical foci or a fine miliary outspread, which appeared during the first fortnight after injection and was absorbed in the course of the following two or three weeks, while a corresponding intratracheal injection caused some almost negligible pulmonary lesions in the lower lobes which, in some cases, persisted, and in others disappeared very soon. Intravenous injection of the virulent strain, on the other hand,

* For reference compare the studies of V. S. Hodson (1932), Pagel (1935), and Opie and McPhedran (1935).

† Several, even ten, times; at least twice.

‡ Kindly supplied by Dr. A. Stanley Griffith.

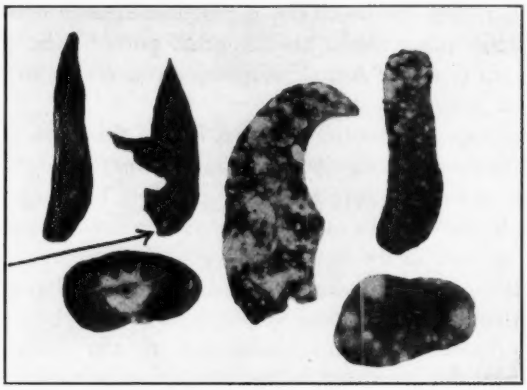

FIG. 1.

Immunity of rabbit 39 (left side of picture)—previously infected intratracheally with 0·1 mg. H37—to intravenous *re*-infection with 0·001 mg. virulent bovine bacilli. Nine weeks after *re*-infection spleen, kidneys, lungs of rabbit 39 free of foci, except for a minute focus near the base of the lung (arrow) due to primary intratracheal infection.

The control rabbit 41 (right side of picture) shows innumerable foci in spleen, lungs and kidneys nine weeks after same intravenous bovine infection as given in rabbit 39.

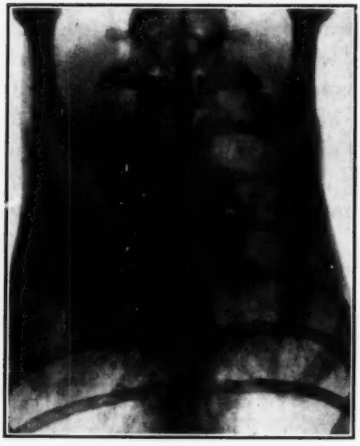

FIG. 2.

Incomplete absorption of miliary tuberculosis in a *re*-infected rabbit. Miliary outspread ten days after virulent *re*-infection (2 mg. H37 intravenously).

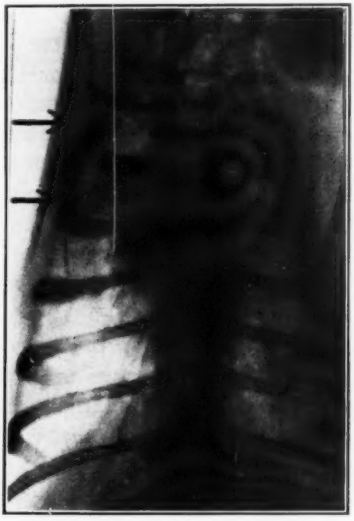

FIG. 3.

Four weeks later outspread incompletely absorbed. A group of miliary foci in the right apex and second intercostal space within an area of infiltration remaining (arrow). "Miliaris discreta."

consistently yielded the picture of extensive generalised tuberculosis with miliary or coarser caseous foci in the lungs and kidneys, an enlarged spleen with innumerable foci, and in the majority of cases, miliary outspreads in the liver. A similar intratracheal injection gave rise to a few fairly small foci in the lung, particularly at the base, and a very slowly progressive tuberculosis, marked by a small number of foci, in the kidneys and spleen.

The severe generalised tuberculosis which, in normal animals, was the consequence of virulent intravenous infection was considerably modified in animals previously infected with human or BCG strains.

According to these experiments repeated intravenous or intratracheal infection with human or BCG strains can confer *immunity against virulent*

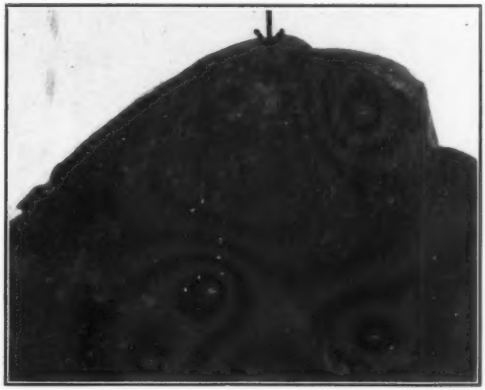

FIG. 4.

Analogous condition in man. "Miliaris discreta" (abortive miliary outspread) in the right apex of a human adult.

reinfection (Fig. 1). In such cases the X-ray film of the lung, after intravenous reinfection with virulent tubercle bacilli, frequently showed a miliary outspread which entirely disappeared within eight to fourteen days, a picture corresponding to that of a healing miliary tuberculosis in man.

When a series of X-ray films displayed a miliary outspread (Fig. 2) which was not completely absorbed at once, but persisted as a discrete miliary outspread in the apex (Fig. 3), being subsequently transformed into strands, (Fig. 5), such a picture could be interpreted as the experimental reproduction of an apical "miliaris discreta," and its sequel the "Fibrosa densa," conditions known in man (Fig. 4) as early mild hematogenous metastases (W. Neumann, 1929; L. Sayé, 1936), and ascribed to an abortive miliary

tuberculosis or generalisation (Pagel, 1933). It is noteworthy that in the rabbit described the discrete miliary foci formed the centres of an "infraclavicular infiltration" which subsequently disappeared, giving place to fibrotic strands.

In rabbits this experimentally produced immunity did not always prove permanent, for in some cases, despite the apparent absorption of the miliary tuberculosis, a fatal outspread subsequently occurred, death being preceded by symptoms of cachexia, whereas in normal animals, under similar circumstances, severe dyspnœa was observed. Apparently the result of immuni-

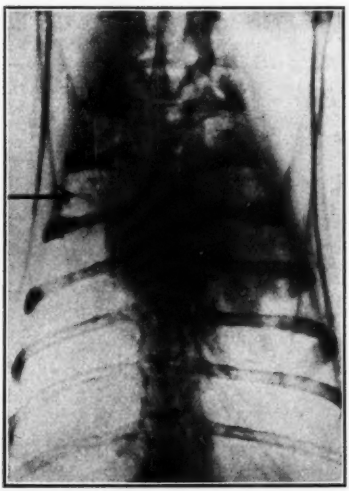

FIG. 5.

Development of the discrete miliary outspread into fibrotic strands (arrow) in the right apical region and second intercostal space of the same rabbit as shown in Figs. 2 and 3. Analogous condition to the "Fibrosa densa" of human adults.

sation depends upon the individual "immunisability" (S. Lyle Cummins, St. A. Griffith) of the animal and the mode and number of avirulent infections preceding virulent reinfection.

A lesser degree of immunity may be assumed in those animals in which reinfection with virulent tubercle bacilli produced a tuberculous process confined almost entirely to the lungs with perhaps slight involvement of the kidneys. (The corresponding infection in the controls was followed by extensive tuberculosis of the lungs, kidneys, spleen and liver.) I first obtained this isolated pulmonary tuberculosis in rabbits by means of reinfection in 1931 (Pagel, 1931), and in the same year Aksjanzew and

Krewer (1931) reported corroborative results which were confirmed by Bieling (1935), and Schwartz (1935).

Since *isolation* of the tuberculous process in the *lung* is the most striking feature of the adult type of human pulmonary tuberculosis, the results of these experiments point to the conclusion that isolated pulmonary tuberculosis in the adult is dependent upon the peculiar allergic condition of an incomplete immunity, which suffices for the protection of the extra-pulmonary organs, but not of the most susceptible of the organs, the lung.

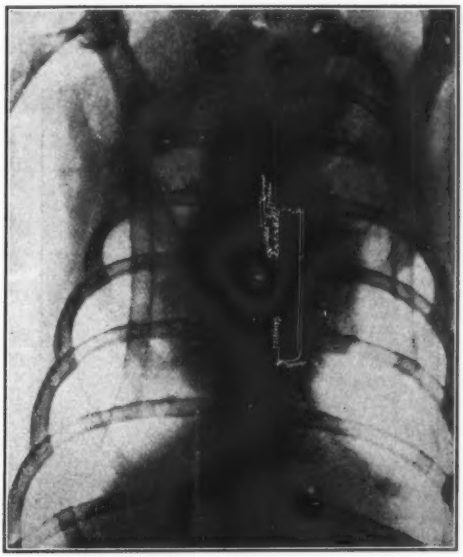

FIG. 6.

" Infraclavicular early infiltration " in the left second intercostal space ten days after avirulent intratracheal *re*-infection (0·1 mg. of a bovine strain with diminished virulence). Previous avirulent intratracheal infection (4 times 1·0 mg. " BCG–S ").

Another important feature of the adult type of early pulmonary tuberculosis is the *formation of confluent focal infiltrations*, especially in the apical or rather subapical regions of the lung (" early infiltrations ").

Such infiltrations were easily obtained (in one to three weeks) by *intratracheal reinfection*, being particularly marked when the primary infection had also been an intratracheal one. They soon disappeared when the bacilli employed for reinfection were avirulent (Figs. 6, 7), but persisted and became caseous (Figs. 8-11) when the bacilli were virulent. In the control animals intratracheal infection produced some small foci in the lung,

which quickly disappeared when the bacilli were of an avirulent strain, or developed into a mild tuberculosis when the bacilli were virulent.

This production of infiltrations, the experimental counterpart of the early foci of the " adult type " of human pulmonary tuberculosis, confirms the results obtained by Baldwin and Gardner (1921), Bieling and Schwartz (1930, 1935), H. S. Willis (1934), H. E. Burke (1935), and more recently by Hutzler-Oppenheimer (1935) in the institute of Rich, and recalls the peculiar lung consolidation described by Cummins and Weatherall as an allergic reaction in rabbits after intravenous injection of human bacilli.

The question which we must now endeavour to answer is: Is the experimental production of these foci by intratracheal reinfection a proof that in

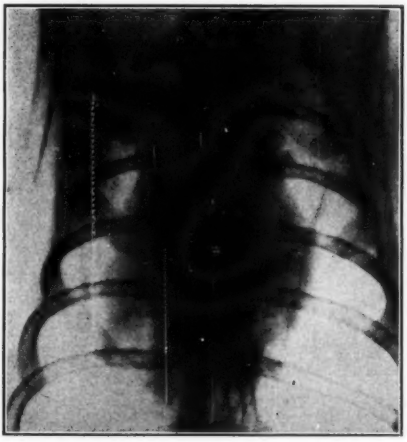

FIG. 7.
Disappearance of infiltration after fourteen days.

adult man they are the result of exogenous introduction of bacilli to the lung (" exogenous reinfection ") ?

It is difficult to believe that any such conclusion is justifiable. Intratracheal reinfection is performed by inserting the syringe into the trachea, pushing it forward toward the bifurcation and injecting a coarse suspension of bacilli. This method can scarcely be regarded as an imitation of physiological infection, and its results, therefore, ought not to be taken as proof of exogenous reinfection, unless they are confirmed by those obtained in control animals which have been allowed to inhale tubercle bacilli in numbers comparable with those presumably inhaled by man during exogenous reinfection.

FIG. 8.

Formation of large "early infiltration" after virulent intratracheal *re*-infection (0·01 mg. of the virulent bovine strain). Twelve days after virulent intratracheal *re*-infection X-ray film showing large confluent shadows, especially on the right side.

(X-ray film showing no foci twelve days after primary virulent intratracheal infection [control rabbit] not shown.)

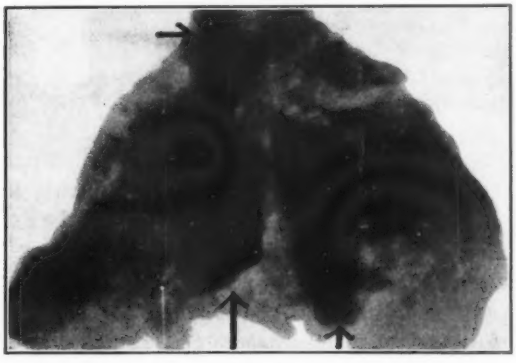

FIG. 9.

X-ray film of lung showing large confluent shadows twenty days after virulent intratracheal *re*-infection.

But one fact these experiments do appear to establish is that early infiltrations in man frequently develop as the result of coarse aspiration from old pulmonary foci, which, having become recrudescent, erupt into the bronchial spaces. On several occasions I have published descriptions of "early infiltrations" in the infraclavicular (subapical and horizontal) regions of the upper lobe in man, which could only be explained as sequela of bronchogenic aspiration either from "strand-cavities" in the apex, too small to be recognisable in the X-ray film, or from partially calcified recrudescent foci with irruptions into the "parafocal" bronchiectatic spaces (Fig. 12). In

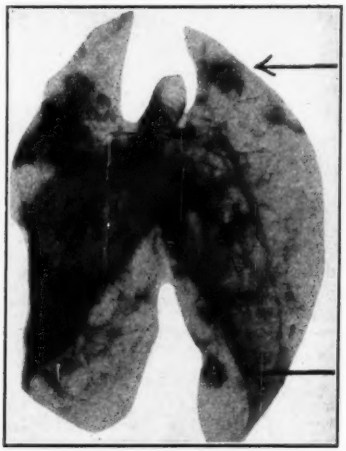

FIG. 10.

X-ray film showing small foci (arrows) twenty days after primary virulent intratracheal infection with 0·01 mg. of the bovine strain (control rabbit).

such cases an aspiration of coarse caseous and liquefied particles rich in tubercle bacilli is the probable cause of subsequent "early foci," and this process, in my opinion, has been successfully imitated by the method of intratracheal reinfection described above.

In the second place, hematogenous metastasis, which usually leads to miliary and supermiliary symmetrical outspreads, may, under special allergic conditions which modify such outspreads, give rise to one or more larger caseous infiltrations analogous to those occurring in isolated pulmonary tuberculosis in adult man. This condition can be illustrated by the intravenous (hematogenous) reinfection of rabbits with virulent tubercle bacilli, similar injections of which produce in normal animals the typical picture of a miliary or coarser symmetrical outspread in both lungs, with very small

areas of normal lung tissue between the innumerable foci. In allergic animals, however, reinfection has a tendency to cause larger foci or infiltrations in the apical, corticopleural and basal regions of the lung only,

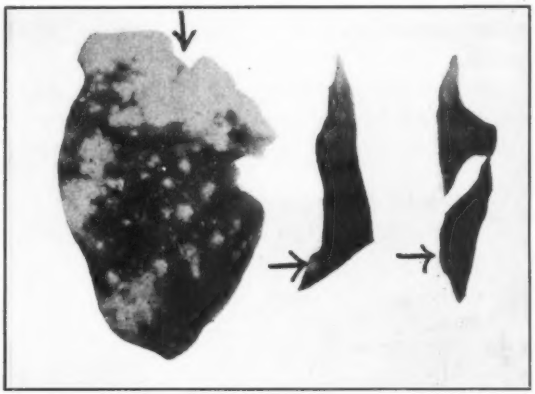

FIG. 11.

Rabbit 29 (left side): Large confluent caseous infiltrations twenty days after virulent intratracheal *re*-infection.

Rabbit 34 (right side): Control, minute foci at the base twenty days after primary virulent intratracheal infection.

FIG. 12.

Discrete miliary tuberculosis in the right upper lobe of a *human* lung. Groups of miliary foci. In addition, caseous bronchitis with "parafocal" bronchiectasis. Irruption of the small caseous bronchitic focus into the "parafocal space" as source of coarse bronchogenic aspiration.

leaving large areas of the organ unaffected. The course of the disease then depends entirely upon the fate of these infiltrations (liquefaction, bronchogenic outspread).

When such reinfection follows intratracheal infection with virulent bacilli, an isolated pulmonary tuberculosis may develop with enormous confluent caseous infiltrations, sometimes similar to those resulting from intratracheal reinfection. In the control animals simple intravenous infection gives the monotonous picture of miliary or supermiliary symmetrical outspreads.

When both infection and reinfection have been intravenous:

1. The localisation of infiltrations in the corticopleural regions may be very marked (Figs. 13-15). Sometimes these infiltrations are obviously remnants

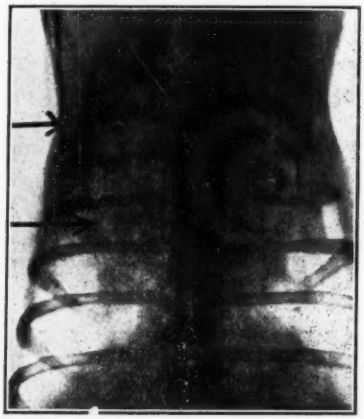

FIG. 13.

X-ray film showing large individual foci and infiltrations of the right lung forty-five days after virulent intravenous *re*-infection (0·01 mg. of the bovine strain). Animal (No. 25) previously twice infected intravenously with 2 mg. "BCG-S."

of a more extensive miliary outspread. In one of our cases only miliary foci with a tendency to confluence and liquefaction persisted at the base of the lung.

2. True infraclavicular foci, very similar to the "circular infiltrations" of man, can be observed (Figs. 16, 17).

3. Liquefying foci and cavities may be obtained resembling liquefying "early infiltrations," and cavities seen in the early stages of adult tuberculosis in man (Figs. 18, 19).

Thus, a lesion corresponding to early pulmonary tuberculosis of the adult type could be produced by means of hematogenous infection and reinfection, from which perhaps we may conclude that transmission of tubercle bacilli by the blood stream may cause early pulmonary tuberculosis in adult man.

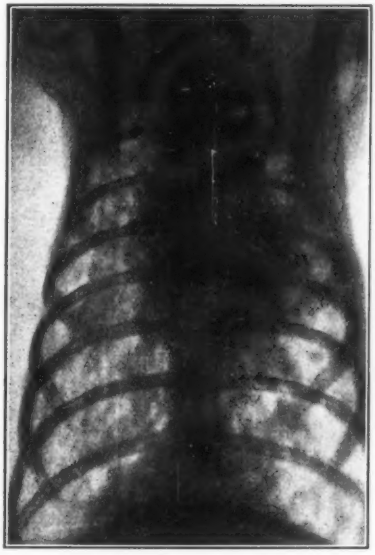

FIG. 14.
X-ray film of the lung of control rabbit (No. 32) thirty-five days after same virulent intravenous infection (0·01 mg. of the bovine strain), showing an even miliary outspread.

FIG. 15.
Corticopleural infiltrations forty-five days after virulent intravenous *re*-infection (rabbit 25, on right side of picture). An even miliary outspread thirty-five days after virulent intravenous infection in the control rabbit 32 on left side of picture.

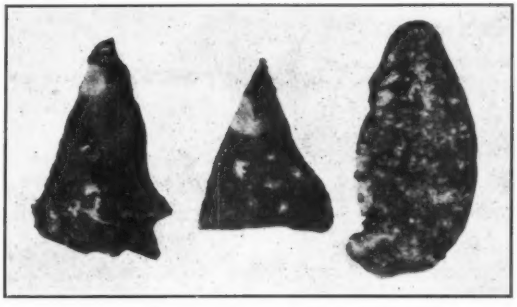

FIG. 16.
"Infraclavicular and circular infiltration" fifty days after virulent intravenous *re*-infection (0·001 mg. bovine bacilli) in rabbit 37 (left side of picture). Control rabbit 40 (right side of picture) shows an even miliary outspread fifty days after same intravenous infection.

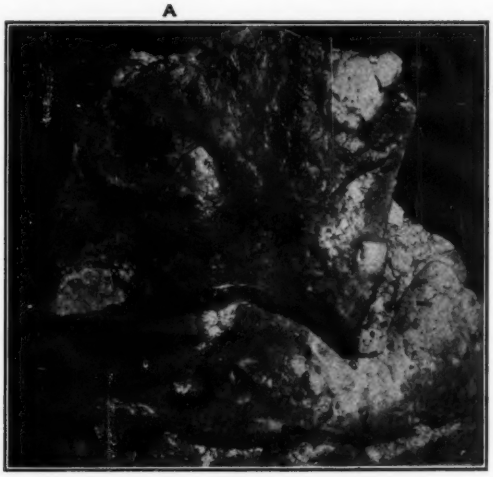

FIG. 17.

"Early infraclavicular infiltration" (I) of man in the right upper lobe (horizontal region; apex [A] not involved). Compare condition with the circular foci produced by intravenous virulent *re*-infection in a rabbit.

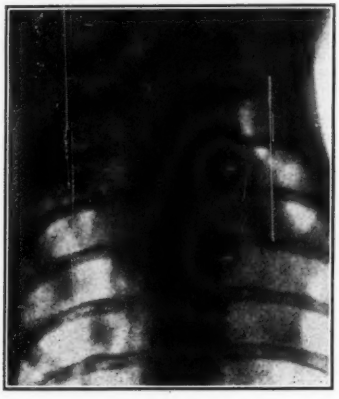

FIG. 18.

X-ray film of "liquefied infiltration" in the right second intercostal space forty days after virulent intravenous *re*-infection (0·01 mg. bovine bacilli). Previously infected ten times with 0·05 mg. of a human sputum strain intravenously.

The various conditions described can obviously be interpreted as representative of the various stages of allergy outlined by Lyle S. Cummins : the large early infiltrations as those of a toxic phase of allergic hypersensitiveness, the circular and corticopleural foci as those of " immuno-allergy " (resulting in a " diminution or cessation of inflammatory and exudative phenomena "), while the limitation of the process to the lung may be regarded as " augmentation of natural immunity."

It must be admitted that a single intravenous injection of certain bovine strains with low virulence can cause in normal rabbits a chronic tuberculosis with pulmonary cavitation resembling the liquefaction of early foci in man,

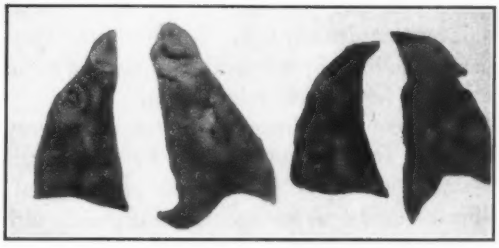

FIG. 19.

" Liquefied infiltrations " forty days after virulent intravenous *re*-infection in rabbit 22 (left side of picture). Control rabbit 21 (right side of picture) shows an even supermiliary outspread forty-five days after same intravenous infection.

but it is a chronic primary tuberculosis with generalisation, which must be differentiated from the post-primary isolated pulmonary lesion of adult man.

The evidence in support of endogenous reinfection as the origin of isolated pulmonary tuberculosis, however, does not necessarily exclude, as auxiliary factors, exogenous reinfection and bronchogenic transmission of bacilli from existing liquefying foci, as demonstrated by experiments in intratracheal reinfection, although the actual development of early foci may not be directly due to bacilli inhaled by the allergic adult organism. Exposure to infection may play a part in the pathogenesis of adult tuberculosis, as Opie and McPhedran (1935) have pointed out, but before exogenous reinfection can be established as the principal factor it is necessary to study the frequency of primary infection in young adults exposed to infection, and the influence of such exposure on the tendency of existing pulmonary lesions to hematogenous metastasis.

Summary.

1. The principal features of early pulmonary tuberculosis in adult man, including limitation of the process to the lung and of miliary outspreads to its apical, corticopleural and basal regions, and the formation of large infiltrations, were reproduced in rabbits by means of intravenous reinfection.

2. Large pulmonary infiltrations were also obtained by intratracheal reinfection.

3. The effects of intratracheal reinfection are apparently comparable with the development of early foci in man by coarse aspiration into the bronchial spaces from recrudescent foci. Intratracheal injection can not be regarded as equivalent to the physiological transmission to the lung of bacilli from an external source (exogenous reinfection).

4. CONCLUSION.—These experiments support the theory that isolated pulmonary tuberculosis in the adult is due to an allergic condition of diminished hypersensitiveness, which limits the pathological process to one organ and modifies extensive hematogenous outspreads into one or more large infiltrations. The fate of the organism depends upon the subsequent development of these early foci.

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THE PHYSIOLOGIC NATURE OF PROTECTIVE AND HEALING PRINCIPLES IN TUBERCULOSIS*

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In considering the therapeutics of tuberculosis two major questions arise: (1) What remedies or measures are effective? and (2) How do they act? Only an understanding of immunological principles will answer these questions.

The host protects itself against all undigested protein which enters the tissues, including those of bacterial origin, by a process of intracellular digestion. This parenteral digestion is carried on by a normal function of cells, but one capable of being stimulated to many times its usual capacity. In this manner the host immunises himself against protein.

Clinical tuberculosis never shows the simple reactions of primary infection, but the more energetic reaction of immunity. We are dealing with a patient whose tissues and reactions have been altered by a previous infection or by the sometime presence of the existent infection; yet in whom, it should be pointed out, there are probably no new reactions, qualitatively, brought in to protect the host, but only quantitative changes in normal cell activity. Even circulating antibodies are those which have been discharged into the circulation from the cells.

The defence phenomena first called forth by the few bacilli usually responsible for the initial infection in tuberculosis fall within the range of normal physiologic activity. However, larger numbers of bacilli, or bacilli which are more virulent, produce extra demands on the cells, and they respond with increased activity. This increased activity is the cause of symptoms of tuberculous disease. Bacilli produce, as a result of their growth in the tissues, and also as a result of their destruction by cellular processes, a substance, complex in nature, which may be called natural tuberculin, in contradistinction to tuberculin made in the laboratory.

Natural and laboratory-made tuberculins are alike in certain particulars. Each contains nucleoprotein, and each contains a soluble carbohydrate

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residue. But natural tuberculin contains some unknown substance, which so far has escaped laboratory elaboration, which stimulates the body cells to a quickened and sometimes a manifold increase in their normal antibody production. We speak of this condition on the part of the cells as sensitisation. Bacilli, living or dead, and tuberculin, natural or made in the laboratory, will react with sensitised cells. This fact is taken advantage of in diagnosis. Nature uses it in protection and healing; and physicians who use tuberculin therapeutically find this the basis for their faith in its action.

The intensified function of body cells toward bacilli and bacillary protein is called allergy. As used in immunology, this term is confusing. It is restricted too narrowly to the inflammatory phenomena which result when antibody and antigen meet in the cells. This separates it from other forms of defence, and by so doing causes a confusion of thought. Allergy simply means altered reaction; not only the altered reaction of a simple function of a cell, but all altered physiologic reactions of cells which are made necessary to oppose infection. If we would consider allergy in this light, it would at once be recognised as a part of the physiologic defence utilised by the host to oppose infection. Probably more would be gained by dropping the word "allergy" altogether, and speaking only of defensive or immunological phenomena.

The defence as a whole consists of (1) hyperæmia at the point of invasion; (2) an increased number of blood and lymph elements being brought to the seat of infection; (3) mononuclear phagocytosis; (4) probably in some instances a hastening of bacilli from the seat of infection and in other cases probably a hindrance to their spread, as recently shown by Lurie;[1] (5) in the intracellular destruction of bacilli by various enzymes; (6) the inhibition of growth of bacilli and possibly other factors which are not definitely known.

The immunological reaction does not appear in primary infection until after cell sensitisation, with other protective phenomena, has developed. However, the fact of the formation of a focus in the tissues, with growth, multiplication, and destruction of bacilli, makes it necessary to protect the host from repeated inoculations, and this requires the body to develop a defensive mechanism which is competent to destroy varying quantities of bacilli and bacillary protein.

Regardless of the vast amount of research which has been carried out in attempting to provide an understanding of defensive factors, there are still many gaps in our knowledge to be filled and much difference of opinion among individual workers to be reconciled.

Zinsser[2] simplifies our conception of protection from bacillary invasion thus: "It seems reasonable to classify both the phagocytic action of the body cells and the formation of antibodies in the blood plasma primarily as

emergency devices for the digestion of foreign materials both formed and unformed; which, under abnormal conditions of injury or disease, penetrate into the physiological interior of the body (blood stream or tissue spaces)."

Long[3] grasps fully the physiologic interpretation of allergy when he says that it is " nothing more than a rapid mobilisation of the same forces which operate in the normal animal." Zinsser[4] states further regarding the immunising mechanism of which the so-called allergy is a part: " The mechanism opposing superinfection is essentially allergic; and such allergy means that the body is on a hair-trigger, as it were, to respond with an energy far more strenuous than the normal reaction to the attack of the specific invader."

The experiments of Zinsser,[5] Dochez,[6] and Swift[7] show that certain organisms may be injected intravenously and produce protection without causing local inflammation when the bacteria again come in contact with the body cells. Their results are quoted as showing that allergy is not necessary to immunity. However, it is manifestly unwarranted, even on the basis of these experiments, to exclude the inflammatory reaction in the allergic animal from being a part of the defensive mechanism.

Inflammatory and General Reaction is Protective.

In order to clarify our idea of the helpful or harmful nature of the inflammatory phenomena associated with the immunologic reaction in tuberculosis, it might not be without interest to discuss inflammation and general reaction, the two phenomena which are so prominent in disease, to see what part they play in the body's defence. Wherever tissues are irritated inflammation follows, and if the irritation is severe, general reaction, as represented by the syndrome of elevation of temperature and other changes in physiologic activity, appears. There is a difference of opinion as to whether inflammation is protective or harmful.

John Hunter (1728-1793) was one of the first among the noted physicians of modern times to expound the protective nature of inflammation. He said: " Inflammation is the reaction to any injury." Bier,[8] by successfully treating various types of inflammation by hyperæmia, which might be considered as an increased inflammation, proved inflammation not to be harmful but beneficial. His work is revolutionary and stands in opposition to the therapeutic principles of combating inflammation with vigour which have been held since the time of Hippocrates. Aschoff[9] also may be mentioned as one who recognises inflammation as a protective and curative agent.

The preponderance of opinion, however, still seems to consider inflammation as the disease rather than the body's method of combating it. This is due to the fact that the symptom-complex composing the disease picture

consists of altered body reactions; and any departure from the usual normal reaction of the body is apt to be considered as wholly harmful. I like to think of the symptom-complex of disease as being *the manner in which the body functions or reacts in the presence of some morbific element or unnatural condition imposed upon it.* It represents two factors: (1) an attempt to maintain the normal functions of the body, and (2) the institution of conditions necessary to meet the abnormal situation created by the presence of morbific factors; both of which are a necessary part of any protective mechanism. It is essentially a symptom-complex of compensating phenomena.

Parenteral Digestion of Bacilli causes Inflammation.

If we consider inflammation in its relationship to parenteral digestion, then we will understand it as a condition which favours the body cells in their function of digesting and carrying away products which may result from injury such as a blood-clot or an exudation in the tissues. We shall also find it helping in the digestion of foreign substances such as protein and bacteria which have found their way into the tissues, either following an injury or having escaped the natural processes of digestion in the gastro-intestinal canal because of entering by way of other portals or through a failure of the gastrointestinal juices to act upon them. This function is similar to, probably identical with, the primitive function which enables unicellular organisms to seize and digest materials which are required for their nutrition.

It is quite evident that a function, normally beneficent, might even become injurious when stimulated to an excessive degree. This sometimes is the case in the quick, violent reaction to the successive entrance of large amounts of bacteria or foreign protein into the tissues.

Probably the severest reactions which take place, however, are mild in their injurious effects upon the organism when compared with the consequences which might follow a failure of the defensive mechanism to function when confronted by large quantities of bacillary or non-bacillary protein.

Since their digestion may be accompanied by both local and general reaction, it seems at least as reasonable to consider these phenomena as a necessary part of nature's method of protecting the organism as to consider them as harmful phenomena. This interpretation is warranted by the fact that the sympathetic nervous system, the glands of internal secretion, the reticulo-endothelial system and the body cells generally, are stimulated to increased activities as a result of their presence. It is further warranted by the localisation of bacteria which is brought about by inflammation; by their destruction through phagocytosis and antibody action; and by the stimulation

of the metabolic activity of the host which results in elevation of body temperature, a condition which enhances chemical reactions.

The fractions of tubercle bacilli which call forth inflammatory reaction to oppose them may escape from tuberculous foci anywhere in the body and stimulate the cells generally to react allergically whenever they or the bacilli from which they are derived again come in contact with them.

This is shown especially well in metastases which form during the course of tuberculosis. No matter in what part of the body they appear, they are quickly opposed by inflammatory phenomena, local and possibly general, which represent a manifold increase in the body's natural protective response. The fact that the inflammation may be severe and that it may be followed by destruction of tissue is sometimes interpreted as meaning that the inflammatory reaction is essentially harmful. On the contrary, this fact may be just as logically interpreted as an indication that the body finds the severe reaction necessary to meet the severe infection. The fact that healing is facilitated by the reaction is suggestive of a favourable interpretation. We see the effect of the failure to react in the prelethal stage of tuberculosis, when the body is no longer able to defend itself with its accustomed energy against the onslaught of bacilli. As a consequence the inflammatory phenomena are less pronounced and sometimes almost absent, and protection is also ineffective.

Clinical Application of Physiologic Measures.

The practical suggestion arising out of this discussion is that protection of the body against infectious disease is primarily a physiologic function, and so the chief aim of the physician should be to make the patient able to maintain the various cells of the body in the condition in which they are able to function in the most efficient manner. This physiologic efficiency will include the body's power to protect itself against infections. While it is not given to any one to know exactly how nature works to protect the individual in case of illness, his understanding will be in proportion to his grasp of the principles which govern normal physiologic function, plus his conception of the nature of the disease from which his patient suffers.

How shall we apply the principles so far discussed to the protection of he tuberculous patient against metastases, and to the healing of any infection which already exists ?

If the conception that inflammation is protective is correct, then one should not worry unnecessarily about the inflammatory reaction in itself. It is a phenomenon which is probably advantageous in localising and destroying invading bacilli. It may be of greatest value to the host early in the disease before a high degree of defence has been developed, even though

it is more apt to cause necrosis of tissue and cavity formation at this time. As a result of the destruction of tissue, bacilli, which otherwise might prove harmful, are expelled from the body, and, as a result of the elaboration of an unusual amount of bacillary substances, the patient's ability to oppose further metastases is greatly enhanced. Later, when a more competent defence has been elaborated, cavity formation occurs relatively less frequently. As the disease extends, the body increases its capacity to accommodate itself to ever larger amounts of bacillary substances with a lessened danger of tissue destruction. At this stage of the infection only unusually large numbers of bacilli produce metastases, and only unusually large amounts of bacillary substances produce excessive reaction. This period of heightened resistance persists during most of the course of chronic tuberculosis.

An early tuberculous lesion, even with cavity, may not be serious if treated properly. Present knowledge forces the early recognition of clinical tuberculosis in order that the measures which are necessary to its healing may be instituted at once. Unless we have a better method of attacking infection than by the allergic response which nature has provided, let us not decry it, but attempt to understand it so that it may be utilised to the patient's advantage. It is not inflammatory reaction of allergy in itself that is harmful, but the unusually severe reaction. Severe reactions might be largely avoided if tuberculosis were diagnosed early and the likelihood of large metastases were reduced by the immediate application of suitable treatment. Destructive cavitation would also be largely prevented thereby.

Now let us assume that spreading of infection is opposed by the allergic reaction; and as a result of previous stimulation of the body cells by bacillary protein the patient has become allergic and his cells are prepared to produce an increased amount of protective substances and are able better to withstand invading bacilli; then, this affords the clinician an opportunity for establishing further important protective measures: (1) by directing the patient's life so that danger of further spreading of the disease may be minimised; and (2) by applying remedial measures for healing the infection which has already taken place.

The greatest factors in preventing further spread of the disease within the lung are: (1) that of reducing circulatory and respiratory effort to a minimum; and (2) that of raising the physiologic response of the patient to the highest possible point of efficiency. The first is accomplished by continuous rest in bed, plus the development of a proper psychology; the second by all of those hygienic measures which have been elaborated since Brehmer's time. Unless metastases are already forming, rarely do we find that early tuberculosis spreads after the patient has been put on a properly planned hygienic

regimen with continuous bed rest. On the other hand, we frequently observe an extension of the disease or an increase in the severity of its reaction, sometimes within a few days, when the patient continues his ordinary activities.

It is the duty of the physician to acquaint himself with the patient so thoroughly that he is able to lay out for him a mode of life which in every way contributes to his maintaining a high physiologic balance. The prescribing of a suitable diet, hygienic living in the open air, the control of visiting and all activities until healing has been completed are among his duties.

Unhealed lesions are accompanied by increased permeability of the vessels which permits of the escape of an increased amount of lymph, with the protective elements which it contains, into the foci. This increased permeability affords an opportunity to apply remedies by way of the blood stream directly to the focus of disease. Nature takes advantage of this fact in applying her own tuberculin and other bacillary products to unhealed foci. Those who use tuberculin therapeutically also take advantage of this situation to stimulate unhealed foci. Tuberculin produces a hyperæmia in tuberculous foci, and in this way brings more protecting substances to the part which inhibit the growth of bacilli, digest them and the focal products, and carry off the residue.

Furthermore, this increased permeability furnishes the basis for the action of gold salts and other stimulating forms of therapy. There is no doubt but that such therapy is of considerable value at times, and there is no doubt but that the remedies are especially able to exert their greatest action upon the tuberculous lesions throughout the body, because of their greater vascular permeability.

The process of healing in tuberculosis consists of destroying as many bacilli as possible; rendering inactive and inert those that cannot be destroyed; clearing the tissues of all products of exudation and destruction; and then converting the remaining elements into new fibrous tissue.

If our patients could all be treated early and ideally, there would be little more to be said about treatment than to control the patient's physiologic balance until healing is consummated. Unfortunately, all are not treated early, nor are all treated ideally; in fact, most patients are treated late, and expediency too frequently dictates the method.

Physiologic Response assisted by Mechanical Aid.

When cavity forms early, and when the disease has been present for a long time and the normal elastic lung tissue has been replaced by scar, or the lung volume has been reduced by actual destruction, then a new factor

enters into healing which, for the moment, often assumes immediate importance. As the volume of lung tissue decreases a disproportion arises between the lung volume and the size of the bony cage, which puts the pulmonary tissues on tension and prevents that compensation which is necessary for healing to take place.

This disproportion may be compensated partly by the lung tissue itself, in which case the non-infected or less seriously infected portions of the lung, and particularly those portions adjoining the diseased areas, take on emphysema and thus make up for that portion of the lung which has been lost by destruction or contraction. Compensation is also made by reduction in the size of the thoracic cage. The ribs assume a more oblique direction; the intercostal spaces become narrower; and the anteroposterior diameter of the chest lessens; all of which decrease the size of the thoracic cavity. The diaphragm, too, at times assumes a higher position than normal. When the mediastinum is free and the destructive disease is confined or predominates in one lung, often the centralateral lung enlarges and, together with the heart, shifts over into the opposite thoracic cavity. By these various compensatory measures taking place, conditions which otherwise would interfere and prevent healing are often remedied by nature alone.

However, nature is not always so competent; and to meet her failure measures have been devised which at least partially relieve the pulmonary tissues of tension and either reduce the size of the thoracic cage or actively compress the lung.

So many patients who might secure healing by physiologic measures alone are being treated successfully by mechanical assistance; and so many who could not secure a healing without aid are securing it by the use of these operative measures that there is danger of our forgetting that healing is a physiologic process and assuming that mechanical aid is required in cases where it is not.

Factors which contribute to this point of view are: (1) the preponderant number of advanced chronic cases which at the present time present themselves for treatment and often cannot secure results except by mechanical aid; (2) the difficulty experienced in general practice in holding the patient's interest long enough to secure healing except by some such measure as the refill of pneumothorax; and (3) the number of patients who must be accommodated in public hospitals where, because of the lack of bed space, they are not permitted to remain for the period of time necessary for healing to take place, but must be returned to the home to mingle with other members of the family and friends. It is generally recognised that ulcerated areas may be closed more quickly by mechanical aid than if left to nature's own method of healing. We must admit that a successful pneumothorax will,

in many cases, close open lesions quicker than the more simple physiologic measures; but in the final analysis there is no successful way of shortening the period of treatment beyond that which nature requires to produce healing. One should always bear in mind that in treating tuberculosis one is treating the patient far more than the disease.

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CLINICAL CASES

COMPLETE RECOVERY FROM MILIARY TUBERCULOSIS OF THE LUNGS

By JAMES MAXWELL,
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The reason for reporting this case in particular detail is that the course of the illness and the ultimate outcome render it almost, if not quite, unique.

The patient was a single girl, aged twenty-two, who was a nurse in one of the L.C.C. mental hospitals, and she first came under my observation on November 15, 1934. Five months previously she had noticed that she was becoming easily tired, especially towards the evening. Although her work required more and more of an effort, she remained on duty and did not report her indisposition. Two months later she developed enlarged glands in the right side of the neck, which were not painful. There was some discomfort in the throat, but no real soreness. A few weeks later similar glands appeared on the left side of the neck. In the beginning of November, 1934, she was sent home to Ireland for a holiday, but instead of feeling better she felt more fatigued, and her throat became definitely sore. She then took her temperature regularly and found that there was evening pyrexia between 100° and 101°. She developed backache and frontal headache. Although she rested continually at this time she did not feel any better and began to develop a dry irritative cough with very little sputum. The appetite was not affected, her digestion was good, the bowels acted regularly, and there had been only a slight loss of weight. The family history was good, with the exception of one sister, four years older than the patient, who had contracted pulmonary tuberculosis at the age of twenty-two. This girl had also been a nurse at the same hospital and had occasionally been in contact with the patient. On November 12 she was referred to the throat department of St. Bartholomew's Hospital. On examination of her throat the tonsils were found to be enlarged and infected. In view of the obvious glands on the neck, an X-ray picture (Fig. 1) was taken of the chest, and

a diagnosis of miliary tuberculosis of the lungs was made on the strength of this. She was therefore admitted to hospital under the care of Professor F. R. Fraser and the writer. On admission she did not look particularly ill, although she was rather flushed. The evening temperature was a little elevated—between 99° and 100°—and there was only a slight rise in the pulse-rate, which settled promptly with rest in bed. The tonsils were definitely enlarged and there was some exudate behind the left tonsil. On both sides of the neck, immediately below the angles of the mandible,

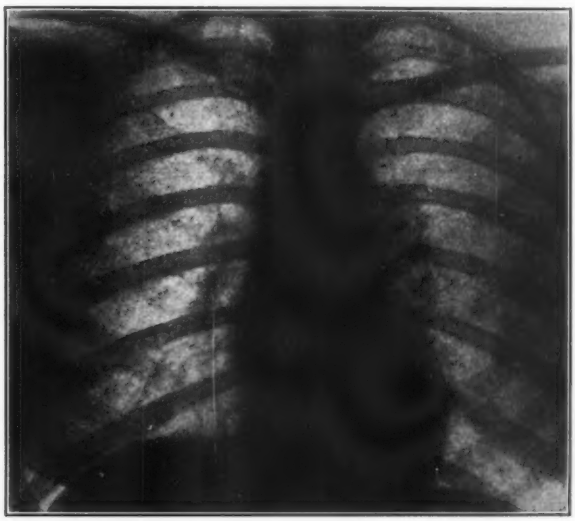

FIG. 1.

January 11, 1935. Typical miliary tuberculosis; enlargement of glands in left hilum.

there were three or four moderately enlarged, hard, discrete glands. These were freely movable, not adherent to the skin and not tender. There was no sign of softening in any of these glands.

The chest appeared absolutely normal and the only physical sign was the presence of occasional crepitations in the right suprascapular region. There was one small soft gland in the left axilla.

The heart appeared normal on examination, and the blood pressure was 110/68.

The abdomen was perfectly normal.

There were no abnormal signs in the central nervous system.

The urine was normal.

In view of the X-ray appearances in the chest the following investigations were carried out:

1. In the absence of sputum, the stools were examined for tubercle bacilli and these were found to be present.

2. The stomach washings were also examined, but tubercle bacilli were not detected.

3. A small specimen of sputum was obtained on November 26, after the patient had been given small doses of potassium iodide for a week, and tubercle bacilli were present in large numbers in this sputum.

4. The blood count showed R.B.C. 5,060,000 per c.mm., W.B.C. 8,800 per c.mm. Hb 95 per cent.

5. Sedimentation rate of the red cells: November 23, 1934, 60 mm. in one hour; January 19, 1935, 76 mm. in one hour; March 2, 1935, 68 mm. in one hour.

It appeared, therefore, quite clear that the condition was one of miliary tuberculosis of the lungs, and a very bad prognosis was given. It is in the subsequent course of the illness that the chief interest of the case is centred. Throughout her stay in hospital her condition remained remarkably good. The temperature for the first two weeks showed a regular evening rise of between 100° and 101°. During the third week it was appreciably lower, only reaching 99·8° on two occasions. During the third week the patient developed an attack of definite tonsillitis and the evening temperature again rose to 101° for a further seven days. This was followed by an interval of ten days of complete apyrexia, after which the temperature again rose to 101° for a further ten days. At this time the temperature chart showed a relapsing pyrexia very similar to that sometimes seen in the Pel-Ebstein type usually associated with Hodgkin's disease, but one of the pyrexial waves, at least, coincided with an exacerbation of the sore throat. The pulse-rate showed a periodicity varying exactly with the temperature.

The weight on admission to hospital was 115½ pounds, and it very slowly fell to 105 pounds in the middle of January, after which it remained stationary, being 107½ pounds on discharge on March 4, 1935.

In view of the very bad prognosis and the complete absence of any effective method of treatment very little was done for the patient, although it was recognised that she was not so ill as are most patients under similar circumstances. The treatment adopted was complete rest in bed, together with 3,000 units of radiostoleum three times daily for a month, and 2 drachm of calcium lactate daily in four doses. The patient developed some digestive troubles and loss of appetite towards the end of December, and the radiostoleum was discontinued in the belief that it might be responsible for the

dyspepsia. The patient certainly seemed better when she was having no medicinal treatment of any sort.

On January 26, 1935, the patient developed an attack of acute tonsillitis, which coincided with the beginning of one of her waves of pyrexia and which must have been largely responsible for it. In view of this and of the good general condition of the patient it was decided, after some hesitation, to advise tonsillectomy, and this operation was carried out on February 12.

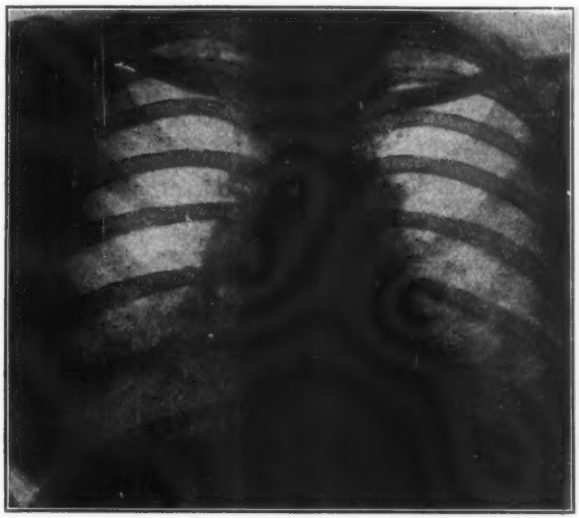

FIG. 2.

February 4, 1936. Appearance of miliary tuberculosis has disappeared and the hilar shadows are within normal limits. There is a little thickening at both apices, especially the right.

There was absolutely no disturbance following the operation and the temperature settled completely after this.

Careful examination of the tonsils after removal failed to yield any evidence of tuberculous infection, either on culture or on microscopic section. The patient was transferred to the Royal National Sanatorium, Bournemouth, in March, 1935, and while there she gained weight and did very well. In August, 1935, she developed some fibrinous pleurisy in the lungs, and there was no sputum at that time. The temperature settled completely after a fortnight. Progress was again maintained, and she was allowed to return to London in February, 1936, to be kept under observation. Since then she has been examined at intervals, and the

surprising feature of the case is the present state as revealed by X-ray examination.

She appears now to be completely healthy and weighs 133 pounds. There are no physical signs anywhere; she can undertake any reasonable amount of exertion without fatigue. The X-ray of the chest is reproduced in Fig. 2, and it will be seen that there has been disappearance of the abnormal shadows with the exception of, perhaps, a small fibrous area towards the left apex.

Comment.

Very few cases are on record in which miliary tuberculosis of the lungs is known to have healed, but in all of them the X-ray of the chest has revealed either gross resultant fibrosis or calcification. The particular interest of this case lies in the completeness of the recovery, for now there are not even radiological signs of the tuberculous infection, and it would be possible to accept the radiogram as normal. There can be little doubt that the condition was caused by a blood-stream infection, the bacilli having entered a radicle of the jugular vein at some point where it was in contact with the glands of the neck. With regard to the ultimate prognosis it is impossible to say, but it seems clear that the patient has established a very considerable immunity to the tubercle bacillus, and there appears to be every reason to believe that she will remain in good health.

ACUTE TUBERCULOUS EPIDIDYMO-ORCHITIS PRESENTING SOME UNUSUAL FEATURES

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THE following case presents an interesting problem in differential diagnosis.

A. F., a labourer aged forty-nine, was admitted to the National Sanatorium, April 15, 1936, with extensive disease of both lungs, temperature range 98°-99° F., pulse 80-88, sputum a trace T.B. positive, sedimentation rate 5·3 after one hour.

On April 17, 1936, he complained of acute pain in the right testicle, and on examination the testis and epididymis were enlarged and acutely tender. There was a small secondary hydrocele, but no thickening of the cord. Per rectum, the prostate and vesicles were normal in size and consistency.

The organ was supported by a sandbag and fomentations applied four-hourly, but the condition remained unchanged. On April 22, 1936, he complained of severe pain in the right knee and metatarso-phalangeal joint of the right great toe, which were found to be swollen, hot and tender, with very slight limitation of movement. There was no rise in the temperature or pulse-rate.

With the appearance of these new symptoms the testicular condition showed a marked improvement, the swelling rapidly diminishing and the organ becoming less tender, though it remained somewhat enlarged and the hydrocele persisted. The cord was now found to be slightly thickened on palpation.

The joint symptoms persisted until April 26, 1936, when they subsided rather rapidly. A period of two weeks' quiescence ensued, followed by a second similar attack lasting a week. After its subsidence, however, some softening was detected in the globus minor of the epididymis, which progressed rapidly to the formation of a cold abscess which ruptured May 20, 1936, discharging typical caseous material containing tubercle bacilli.

Discussion.

When first seen there were two possible diagnoses. The patient's previous profession (a sailor), the clinical picture, and the site of the arthritis were all strongly in favour of a diagnosis of acute gonorrhœal epididymo-orchitis with secondary arthritis. The improvement of the genital condition with the onset of joint symptoms was another point in favour of such a diagnosis.

On the other hand, the patient's strenuous denial of any urethral discharge and the absence of prostatic threads in the urine made such a diagnosis improbable. The second factor was the most easy to assess, and, together with the patient's lung condition, suggested an alternative diagnosis of tuberculous epididymo-orchitis, which was strengthened by the thickening of the cord later, and finally clinched by the formation of a cold abscess.

Choyce, in his *System of Surgery*, states that acute tuberculous epididymo-orchitis may very rarely be associated with a urethral discharge, but makes no mention of articular symptoms.

This case illustrates very well the old axiom " Never make two diagnoses when one will serve."

I am greatly indebted to Dr. C. E. H. Anson, Medical Superintendent of the National Sanatorium, Benenden, for his permission to publish the above case.

CONSULTATION

CASE

By A. TUDOR EDWARDS,
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Surgeon to Westminster Hospital and to Brompton Hospital for Consumption and Diseases of the Chest.

Miss D. D., aged thirty, was admitted to Brompton Hospital under the late Dr. Batty Shaw on November 14, 1932. She stated that three months earlier she had caught cold, which had resulted in cough and expectoration. This continued for several weeks, and tubercle bacilli were subsequently found in the sputum. The family history was negative, except for a brother who had pulmonary tuberculosis.

On examination she was found to have physical signs of a large cavity at the left and several small ones at the right apices respectively. Right artificial pneumothorax was successfully induced, but unfortunately the apex of the left lung was found to be adherent, and, subsequently, left phrenicectomy was carried out with the hope of improving the condition there.

She was readmitted on April 4, 1934, with persistence of positive sputum, when the cavity at the left apex was found to be little altered in size and the condition of the right lung unaltered. It was suggested that apicolysis should be performed to collapse the cavity at the left apex, but this was considered inadvisable as the outer wall of the cavity contained very little pulmonary tissue and was probably deriving its blood supply partially from vessels in the chest wall. Separation of the lung at the apex would thereby rupture these vessels and would almost certainly result in necrosis of the outer wall, with eventual " breaking through " of the wax into the apical cavity. Under these circumstances, upper thoracoplasty appeared to be the operation of choice, and this was performed in two stages, the upper three ribs being removed at the first stage and, a fortnight later, portions of ribs 4-6, the total removal of rib being 42 inches.

Convalescence was uninterrupted, and the patient was discharged to a sanatorium with the cavity diminishing in size.

This operation resulted in a marked improvement in the general condition of the patient, but in November, 1935, she still had a morning cough with

1 to 3 drachms of purulent expectoration which was still T.B. positive. Radiological examination showed the cavity still present in the left upper lobe beneath the operated area. Likewise multiple small cavities with fibrosis were present at the right apex. Further examination of the radiograms showed a marked deviation of the trachea to the *right*. It was now obvious that the retraction and fibrosis on the right side had prevented the closure of the apical cavity after thoracoplasty by pulling over the mediastinum, including the trachea, to the right. The problem for solution was to discover the best means of closing the cavity at the left apex. Was apicolysis, now that the walls had thickened and become fibrosed, advisable at this stage?

It appeared that, if this operation were undertaken, it would merely allow a further retraction of the mediastinum to the right and, probably, would not result in collapse of the left apical cavity. Secondly, it appeared probable that some of the positive sputum was coming from the right side. In view of this it was considered that an upper thoracoplasty on the right side would not only lead to obliteration of the small cavities in that region, but would also allow the trachea to become central in position and thereby help in the closure of the persistent left apical cavity.

With this object in view a two-stage right upper thoracoplasty was carried out on May 25 and June 8, 1936, when thirty inches of the upper five ribs was removed. This resulted in a return of the trachea to the middle line, closure of the right apical cavities, and a slow and steady diminution in the size of the left apical cavity, with almost complete cessation of expectoration. The patient was discharged to a sanatorium doing well on August 11, 1936.

Summary.

This case illustrates several important points. Firstly, the risk of performing apicolysis where there is practically no lung tissue between the cavity and the chest wall. It is now recognised that the outer wall of a pulmonary cavity with little or no radiological evidence of pulmonary tissue derives a secondary blood supply from the chest wall itself, and interference with this vascular supply, as is essential in performing apicolysis, will often be sufficient in association with the presence of the wax to result in pressure necrosis of the outer wall of the cavity, penetration of the wax into the cavity, and its eventual expectoration in small quantities.

Secondly, it illustrates the comparatively poor results that may be expected from a phrenicectomy in cases in which there is marked fibrosis around an apical cavity. Where the cavities, however, are very thin-walled and fibrosis is minimal, temporary phrenicectomy will often result in their closure, after which the operation should be made permanent.

Thirdly, it illustrates the fact that relaxation of one cavitated apex may result in retraction of the mediastinal structures when fibrotic cavitatory disease is present at the opposite apex and, in some cases, to such a degree as to prevent closure of the cavity on the operated side. In many cases, however, in which bilateral apical thoracoplasty has appeared advisable, the performance of the operation on the side to which the mediastinum, trachea, etc., are displaced will often result in the closure of minor cavitation at the opposite apex, and it is advisable, therefore, to wait several months before contemplating an apical thoracoplasty on the second side, as it may eventually be found unnecessary.

THE TUBERCULOSIS ASSOCIATION

PROGRAMME FOR 1936-7.

LONDON MEETINGS

November 20th, 1936.	Presidential Address.	Dr. S. Roodhouse Gloyne.
February 19th, 1937.	Simple Pleural Effusion.	Dr. W. J. Fenton. Dr. E. H. Hudson.
	Life Insurance and Tuberculosis.	Dr. Otto May.
May 21st, 1937.	Bovine Tuberculosis in Man.	Dr. A. S. Griffiths.
	Radiological Classification of Pulmonary Tuberculosis.	Dr. James Watt. Dr. Burton Wood.

PROVINCIAL MEETING AT MANCHESTER

June 10th, 1937.	How long should Collapse Therapy be Delayed?	Dr. G. Marshall. Mr. H. Morriston Davies.
	The Use of the Tomograph.	Dr. J. B. McDougall.

ANNUAL DINNER

June 11th, 1937.	My Chief Difficulties in dealing with the Tuberculosis Problem.	A Consulting Physician. A General Practitioner. A Tuberculosis Officer. A Medical Superintendent. A Prison Medical Officer.
June 12th, 1937.	Artificial Pneumothorax in Children.	Dr. C. D. S. Agassiz.
	Problem Cases Presented by	Dr. E. H. A. Parks. Dr. G. Jessel.

ANNUAL MEETING

CORRESPONDENCE

To the Editor of "The British Journal of Tuberculosis."

INTESTINAL TUBERCULOSIS

Sir,

I read with great interest a summary of the discussion that took place on Intestinal Tuberculosis at the meeting of the Tuberculosis Association held on January 17, 1936, and published in the February number of *Tubercle*.

Dr. Maxwell has attempted to classify the intestinal lesions into different types which to a clinician would appear to be what I should like to describe as a "pathological nicety." From the clinician's point of view, it should be sufficient to classify intestinal tuberculosis into two varieties—namely, (1) primary or hyperplastic and (2) secondary or ulcerative, the latter being a very common complication of the disease in the lungs.

Dr. Maxwell has advocated the use of gold in the treatment of intestinal tuberculosis, but Dr. Heaf thinks it is contraindicated. The question is a debatable one. It appears to me that the results of gold treatment depend upon the type of intestinal tuberculosis that is being treated.

Like the kidneys, the intestine is an important organ through which a large proportion of gold is excreted, and gold, being a heavy metal, is liable to exert its toxic effects on these organs.

Secondary tuberculosis of the intestine is a manifestation of Koch's phenomenon, and is therefore frankly ulcerative, and I am not sure if gold will do any good in this type. There is not much reactive fibrosis in the ulcerative type, and one of the important functions of gold treatment is to stimulate the formation of fibrous tissue in the diseased parts. When, therefore, ulceration is present in the intestinal walls with consequent mucous discharge, gold is not likely to do any good. It may even irritate the mucous membrane and make the condition worse.

It is possible that the good results obtained by Dr. Maxwell were due to the fact that the cases treated by him were "toxæmic" in nature, as pointed out by Dr. Burrell, and were not cases of tuberculous ulceration of the intestine.

On the other hand, gold is well worth trying in the primary type of intestinal tuberculosis, and may give satisfactory results owing to the stimulation of fibrous tissue in the diseased parts.

In India, where infection by the bovine tubercle bacillus is non-existent for all practical purposes, intestinal tuberculosis occurs in a large number of cases suffering from tuberculosis of the lungs. Racial immunity in this country has not yet developed to any appreciable extent, and therefore,

owing to the lack of innate resistance on the part of patients, the disease spreads sooner or later to the intestines from the lungs. One of the reasons why we do not get such good results from gold treatment in pulmonary tuberculosis in this country as are obtained in the Western countries is perhaps due to the fact that the intestinal complication is associated in some degree with the disease in the lungs.

Yours, etc.,

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EDITORIAL NOTE

Drs. Toussaint and MacIntyre in their article on the " Sources of Infection in Primary Tuberculosis of Childhood " which appeared in our July number stated that in a series of 38 cases of tuberculous meningitis Drs. Munro and Scott found that 40 per cent. were due to the bovine type of bacillus. The series was in fact 50 cases, and 36 per cent. (not 40) were due to bovine bacilli.

We much regret this error, but are glad it was discovered in time to incorporate the correct figures in the reprints of the article.

REVIEWS OF NEW BOOKS

Johannes de Mirfield. His Life and Works. By Sir Percival Horton-Smith Hartley, C.V.O., M.A., M.D., F.R.C.P., Consulting Physician to St. Bartholomew's Hospital and to the Brompton Hospital, and sometime Fellow of St. John's College, Cambridge; and Harold Richard Aldridge, M.A., formerly Scholar of Peterhouse, Cambridge. Assistant Keeper in the Department of Manuscripts in the British Museum. Pp. 191. Price 15s. Cambridge University Press, 1936.

John Mirfield was a priest who lived in the Priory in Smithfield and died in 1407. A man of wide reading, he made a special study of medical literature, and for the benefit of mankind wrote what one may describe as abstracts. The authors of this fascinating book have calculated that the printing of the Latin text of the Breviarium alone would fill a volume of 2,450 pages.

In a preface Sir Percival Hartley says that the chief labour in preparing this work fell upon Mr. Aldridge, to whom chief credit is due; and one can indeed appreciate the enormous amount of work involved in searching the records, collating and translating the medieval Latin texts. We hope that both authors will feel that they have not laboured in vain, for the satisfaction of having produced such a work must be great.

After the introduction, in which the life and activities of Johannes as a medical writer are discussed, extracts from the *Breviarium Bartholomæi* and the *Florarium Bartholomæi* are given. The Latin text is printed on the left-hand page with the English translation opposite. Chapter iv. of the Breviarium will prove of special interest to our readers, as it deals with phthisis and indicates the views held in the fourteenth century on the problem of tuberculosis of the lungs. Johannes says that the word "phthisis" used in connection with disease does not mean merely wasting of the body, but is restricted to wasting associated with ulceration of the lung. The difficulties of prognosis are appreciated, and we are told that great caution must be exercised because "sometimes whilst speaking these patients die, and whilst dying they converse."

Clubbing of the fingers, pneumoliths, and bronchial casts are described, and the latter were thought to be veins. Treatment was either curative or palliative, and the number of cures in those days appears to have been even greater than the number on the market today.

There are four plates of portions of the old Latin text and appendices containing notes on the MSS., abstracts from deeds and documents referred to in the text. The book concludes with a useful index. The authors are to be congratulated on having written a very delightful book.

La Pratique du Pneumothorax Thérapeutique. By F. DUMAREST, P. LEFÈVRE, H. MOLLARD, P. PAVIE, and P. ROUGY. Fourth Edition. Pp. 474. Price 50 f. Paris: Masson et Cie, 1936.

The fourth edition of this well-known work will be welcomed by all who know the earlier editions.

After a full discussion of the mechanics of pneumothorax, the authors describe a number of apparatuses and the technique of the initial and subsequent refills. We are surprised to find that they still advocate the use of nitrogen, which in most countries has been entirely supplanted by ordinary air.

They are of opinion that high pressures compress the air and not the lung, and are to be avoided. The optimum pressure is usually one which is zero at the end of expiration.

It is said that the lobes of the lung collapse independently of each other and that the upper lobe collapses partly by gravity. An apical adhesion may be an advantage.

The authors think that the risk of effusion is increased by using too large a needle, by high pressures, or if the pneumothorax is inefficient owing to adhesions. When an effusion develops they advocate leaving it alone during the acute stage, and if severe dyspnœa occurs would remove air rather than liquid. The pages dealing with bilateral pneumothorax are of special interest, and they describe the technique and modern procedure under which so many cases nowadays prove successful. The importance of maintaining the equilibrium of the mediastinum is stressed, and there should not be too great a difference between the pressures on the two sides.

Contralateral artificial pneumothorax, by which is meant the collapse of the healthy lung when the other is adherent, can be of use only if there is a mobile mediastinum.

The authors think that oleothorax has its place in treatment, but is often dangerous and should be used only seldom and in specially selected cases, and with this opinion the majority of modern authorities will agree.

In the concluding chapters is a brief description of the various surgical methods of collapsing the lung or of aiding artificial pneumothorax.

The book is well produced and illustrated and is a standard work on the subject.

Infra-Red Irradiation. By WILLIAM BEAUMONT, M.R.C.P.(Eng.), L.R.C.P. (Lond.). Pp. 140. Price 6s. 6d. London: Lewis and Co., 1936.

This little book gives a clear account of treatment by infra-red irradiation, a term which the author prefers to the older but misleading one radiant heat.

The first half of the book deals with the theories of radiant energy, different wavelengths and the various apparatuses used to supply them. The author is to be congratulated on explaining so clearly the principles of his subject in such a brief space.

When dealing with treatment the most important function is the relief of pain.

An analysis of 1,000 cases treated in this way is given, and the effects on infra-red irradiation of bacteria and body temperature are described.

In the concluding chapter mention is made of the uses of other spheres of infra-red rays. In photography they may demonstrate markings not visible to the naked eye or show that two different sorts of ink have been used in a document which to the eye appears to have been written by one only.

The invisible beam used to guard art collections, rays used by ships to detect icebergs or other ships in fog, rays which operate electric bells or lamps are examples of the practical possibilities of infra-red rays.

Tuberculosis. By GERALD B. WEBB, M.D. Pp. 205, with 17 illustrations. Price $2. New York: Paul B. Hoeber, Inc.

The Clio Medica is a series of works on the history of medicine edited by Dr. E. B. Krumbhaar, and this is one of the series dealing with tuberculosis. Although small enough to be carried in the pocket, the book contains a mass of information, and the author has succeeded in giving a complete survey of the history of tuberculosis and in presenting it in a clear and readable way.

Medicine has made so many advances in recent years that one is apt to feel over-satisfied. It is wholesome to be reminded that we do not know so very much more than Hippocrates, who lived 400 years before Christ. True we have sanocrysin, but they used the lungs of the hog, etc., and " to know if the remedy is good one chews a little, runs for an hour and if one does not vomit the remedy is good."

It was recognised from the earliest times that recovery was possible, and many distinguished physicians were themselves consumptives, including Laennec, Bayle, Bicket, and Christopher Bennet.

Treatment today is often more dramatic, but pulmonary tuberculosis remains a very serious disease, especially, as in the olden days, amongst the young.

The book is well arranged, not in chronological order, but in chapters each dealing with some aspect of the disease such as epidemiology, pathology, diagnosis and treatment.

The illustrations are most interesting, and the book concludes with a bibliography, general index, and index of personal names.

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